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American Heart Journal

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Original Communications

RELATIVE VALUES OF TECHNIQUES USED IN DETECTION OF HEART DISEASE

EDWARD PHILLIPS, M.D., JOHN M. CHAPMAN, M.D., M.P.H., AND
L. S. GOERKE, M.D., M.S.P.H.

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A CARDIAC survey developed with the assistance of the National Heart Institute, the California State Department of Public Health, and the Los Angeles Heart Association, is being conducted by the Los Angeles City Health Department. One purpose of the survey is to determine the most practical means for detection of heart disease capable of mass application. This is a preliminary report of case-finding techniques employed in the initial examination of 2,252 individuals. The subjects were selected at random from 20,199 Los Angeles City employees. The sample was stratified by age, sex, and job classification. Re-examination of each person at approximately eighteen months intervals for eight to ten years is planned. A report of the entire cardiac survey project will appear elsewhere.¹

The mean age of the subjects was 43.7 years. There were 372 people under the age of 30; of the total number, 1,859 were men and 393 were women; 1,899 were of the Caucasian race. (Table I)

TECHNIQUES

Each subject answered a questionnaire history form, and then was seen by a physician who obtained a medical history. Physical examination (excluding rectal and pelvic) was made. The tests of each individual included: a twelve or thirteen lead electrocardiogram, fluoroscopy of the chest, electrokymogram, 70 mm. minifilm of the chest, vital capacity determination, urinalysis, complete blood count, sedimentation rate, hematocrit, serologic test for syphilis, serum cholesterol, and a fasting blood sugar test. In addition, through the courtesy of

From the Los Angeles City Health Department Bureau of Medical Services. Cardiologist (Dr. Phillips), Epidemiologist (Dr. Chapman), Director, Bureau of Medical Services (Dr. Goerke), George M. Uhl, M.D., Health Officer.

This study is aided by a grant from the National Heart Institute, Public Health Service, Federal Security Agency through the Chronic Disease Bureau, California State Department of Public Health.

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TABLE I. NUMBER OF PERSONS EXAMINED IN CARDIAC SURVEY BY AGE, SEX, AND RACE

SEX	RACE	AGES						TOTAL
		0-19	20-29	30-39	40-49	50-59	60-	
Men	White	0	196	358	382	414	200	1,550
	Negro	0	74	99	64	47	16	300
	Oriental	0	0	2	1	0	0	3
	Other	0	3	2	0	1	0	6
	Total	0	273	461	447	462	216	1,859
Women	White	3	71	82	102	74	17	349
	Negro	1	16	10	5	2	1	35
	Oriental	0	6	1	0	0	0	7
	Other	0	2	0	0	0	0	2
	Total	4	95	93	107	76	18	393
Grand Total		4	368	554	554	538	234	2,252

John W. Gofman, M.D., University of California, 849 subjects 40 years of age and older had determinations of Sf 10-20 serum lipoprotein molecules. In subsequent examinations all patients over 39 years of age will have lipoprotein determinations.

The special questionnaire history form is shown in Table II. Questions 1 to 7 are intended to elicit major symptoms of heart disease and/or cardiac decompensation. Questions 8 through 17 may be regarded as past history. Question 9 refers to previously known heart disease. The questionnaire includes four questions regarding familial cardiovascular disease. The answers were transferred to International Business Machine tabulation cards for statistical analyses and correlations.

All the physical examinations were performed by internists. Inasmuch as the value of any survey obviously depends upon the accuracy of the examiners, all observations were made with care and with attention to uniformity. In difficult, unusual, or borderline cases, two or more physicians examined the subject. Auscultation was occasionally checked by phonocardiograms. If the subject was nervous, or the examiner doubtful of his observations, re-examination was made later. Each observation on physical examination was recorded and transferred to IBM cards.

Fluoroscopic examinations were usually performed by the physician who examined the patient. Here, again, in doubtful or unusual cases two or more physicians were consulted. At the discretion of the fluoroscopist, teleoroentgenograms, with or without oblique and lateral views, were ordered in addition to the minifilm which was routine in all subjects. Barium was used in fluroscopy when indicated. Orthodiagrams were rarely made. The electrocardiograms and the electrokymograms were read by one of us (E.P.) independently and without knowledge of the subject. The criteria of the American Heart Association were followed.² The electrokymograms were interpreted according to the criteria of Boone and associates.³ The results of the readings were tabulated on IBM

cards. The 70 mm. minifilms were read in a routine manner by chest physicians who had no knowledge of whether or not any film came from the cardiac survey project.

DETECTION OF HEART DISEASE

Of the 2,252 examined, 162 individuals had heart disease, a discovery ratio of 7.2% (Table III). This excludes patients who had hypertension without heart disease, arteriosclerosis of the aorta, retinal arteriosclerosis or peripheral vascular disease without evidence of heart disease. Criteria of the American Heart Association for the diagnosis of heart disease were rigidly followed. The data reveal that the frequency of heart disease in this group increases abruptly in persons 50 years of age and over.

Hypertensive heart disease was the most common type (95 cases). There were fifty-three persons with coronary arteriosclerotic heart disease and twenty-five with rheumatic heart disease. There were four cases of syphilitic heart disease, one cor pulmonale, two congenital, and one thoracic heart disease. Among the "unknown" types of heart disease, there were seven cases of pericarditis, five of whom were asymptomatic,⁴ and five cases of cardiomegaly without demonstrable cause (Table IV). Thirty-one persons had more than one type of cardiovascular disease.

In addition to those with demonstrable heart disease, there were eighty people (3.6%) with potential or possible heart disease (Table V). Included in the "potential heart disease" group are persons with a history of rheumatic fever or chorea, a questionable history of rheumatic fever and a faint systolic murmur, and those with hypertension and questionable slight cardiac enlargement. Included in the "possible heart disease" group are individuals with a questionable history of angina pectoris, two with auricular fibrillation of undetermined cause, two persons in whom left bundle branch block was demonstrated and two with questionable history of old myocardial infarction. Particular attention will be given to those persons with potential or possible heart disease in the follow-up studies. Undoubtedly many will be reclassified as confirmed heart disease in the future.

RESULTS WITH VARIOUS TECHNIQUES

The blood tests, urinalyses, and vital capacity determinations did not contribute to cardiac case finding. Fifty-nine of the 849 people who had Gofman lipoprotein tests had heart disease. No significant difference was found between the mean levels of the Sf 10-20 lipoproteins in those with heart disease as compared to those without heart disease. Complete data regarding the diagnostic and prognostic value of the lipoprotein levels of the species Sf 10-20, Sf 20-100 and Sf 100-400 with arteriosclerosis and heart disease will be published later. Table VI shows the cardiac abnormalities found by the questionnaire history form, physical examination, electrocardiogram, electrokymogram, fluoroscopy, and minifilm. An answer on the history form which indicated that a symptom suggestive of heart disease was present was considered "positive." Eighty per cent of all cardiac diseases discovered in this survey had evidence of the disease in the

TABLE II.

LOS ANGELES CITY HEALTH DEPARTMENT

CARDIAC STUDY
HISTORY FORM

CONTROL NUMBER

DATE

Mo.

Day

Year

NAME

1. Can you walk a reasonable distance outdoors without trouble? 1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No	12. Have you ever had any of the following: <input type="checkbox"/> Rheumatic Fever? <input type="checkbox"/> Inflammatory rheumatism with swollen or tender joints? <input type="checkbox"/> Chorea or St. Vitus Dance? <input type="checkbox"/> Frequent nose bleeds as a child? <input type="checkbox"/> Asthma <input type="checkbox"/> Syphilis <input type="checkbox"/> No to all questions in above	If yes, at what age did it begin?
2. Do you ever have distress, pain, or an uncomfortable feeling in the chest while walking on the street or up inclines or steps? 1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No If yes, at what age did you first notice it?		
3. While walking are you forced to stop in order to rest? 1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No If yes, is it because of: <input type="checkbox"/> Distress in the chest? <input type="checkbox"/> Shortness of breath? <input type="checkbox"/> Both?		
4. Have you noticed increasing or undue shortness of breath with exertion? 1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No If yes, at what age did you first notice it?		
5. Is your sleep disturbed because of: A <input type="checkbox"/> Coughing spells? <input type="checkbox"/> Difficulty in breathing when lying flat in bed? <input type="checkbox"/> Asthma attacks? <input type="checkbox"/> Choking sensation in the chest? B <input type="checkbox"/> No to all questions in A, above	13. Have you ever been diagnosed as having thyroid trouble? 1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No If yes, at what age was it first diagnosed?	
	14. Have you ever been diagnosed as having kidney trouble or Bright's Disease? 1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No If yes, at what age was it first diagnosed?	
	15. Have you ever been diagnosed as having Diabetes? 1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No If yes, do you take insulin? 1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No	
	16. Were you a blue baby? 1. <input type="checkbox"/> Yes 2. <input type="checkbox"/> No	

17. Were you supposed to have had anything wrong with your heart when you were born? 1. ☐ Yes 2. ☐ No

FAMILY HISTORY

(Family includes mother, father, brothers, sisters, grandparents, aunts and uncles)

1. Have any members of your family, either dead or alive, ever had Rheumatic Fever or Rheumatic Heart Disease?

1. ☐ Yes 2. ☐ No 3. ☐ Do not know

If yes, list relationship and age diagnosed: _____

2. Have any members of your family, either dead or alive, ever had high blood pressure?

1. ☐ Yes 2. ☐ No 3. ☐ Do not know

If yes, list relationship and age diagnosed: _____

3. Have any members of your family, either dead or alive, ever had a stroke?

1. ☐ Yes 2. ☐ No 3. ☐ Do not know

If yes, list relationship and age diagnosed: _____

4. Have any members of your family, either dead or alive, ever had heart trouble?

1. ☐ Yes 2. ☐ No 3. ☐ Do not know

If yes, list relationship and age diagnosed: _____

6. Have you ever had palpitation of the heart? 1. ☐ Yes 2. ☐ No

If yes, at what age did it begin? _____

7. Are your ankles swollen at bedtime? 1. ☐ Yes 2. ☐ No

If yes, at what age did you first notice it? _____

8. Have you ever had high blood pressure diagnosed by a doctor?

1. ☐ Yes 2. ☐ No

If yes, at what age was it first diagnosed? _____

9. Have you ever had heart trouble diagnosed by a doctor?

1. ☐ Yes 2. ☐ No

If yes, was it: _____ At what age was it first diagnosed? _____

☐ A heart murmur?

☐ Heart valve trouble?

☐ Rheumatic heart trouble?

☐ Heart failure?

☐ Coronary thrombosis?

☐ A heart attack?

☐ Do not know?

10. Have you ever taken digitalis? 1. ☐ Yes 2. ☐ No

If yes, when did you start? _____ (year)

Are you still taking it? 1. ☐ Yes 2. ☐ No

11. Have you ever taken nitroglycerin?

1. ☐ Yes 2. ☐ No

If yes, when did you start? _____ (year)

Are you still taking it? 1. ☐ Yes 2. ☐ No

TABLE III. NUMBER AND PER CENT OF PERSONS IN CARDIAC STUDY WITH DIAGNOSED CARDIAC DISEASE BY AGE, SEX, AND RACE

SEX	RACE	AGES					TOTAL	PERCENT CARDIAC DISEASE
		20-29	30-39	40-49	50-59	60-		
Men	White	2	10	17	46	43	118	7.5
	Negro	1	7	7	8	3	26	8.3
Total		3	17	24	54	46	144	7.6
Percent Cardiac Disease*		1.1	3.7	5.4	11.5	20.8	7.6	
Women	White	1	1	1	11	2	16	4.6
	Negro	0	1	0	0	1	2	5.7
Total		1	2	1	11	3	18	4.6
Percent Cardiac Disease*		1.0	2.2	0.9	14.5	16.7	4.6	
Total Men and Women		4	19	25	65	49	162	7.2
Percent Cardiac Disease,* Men and Women		1.1	3.4	4.5	11.9	20.5	7.2	

*Per cent of total in each age group, sex, race in entire population of 2,252.

history. Ninety-four per cent of those with coronary arteriosclerotic heart disease, 60 per cent of those with rheumatic heart disease and 52 per cent of those with hypertensive heart disease were "positive" through the history. Thirty-three and seven-tenths per cent of the cardiac patients had prior knowledge of heart disease. Omitting these known cases, the history form was sensitive in only 62 per cent of the cardiac cases. The problem of specificity and false-positives will be discussed later.

TABLE IV. TYPE OF CARDIAC DISEASE BY AGE AND SEX

TYPE	AGE	20-29		30-39		40-49		50-59		60-		TOTAL*
	SEX	M	F	M	F	M	F	M	F	M	F	
Hypertensive		0	0	4	0	15	1	38	10	25	2	95
Coronary Arteriosclerotic		0	0	2	0	5	1	22	2	20	1	53
Rheumatic		3	1	7	2	2	0	8	0	2	0	25
Syphilis		0	0	1	0	0	0	0	0	3	0	4
Cor Pulmonale		0	0	1	0	0	0	0	0	0	0	1
Congenital		0	0	0	0	1	0	1	0	0	0	2
Other		0	0	0	0	0	0	1	0	0	0	1
Unknown		0	0	7	0	3	0	2	0	0	0	12
Total*		3	1	22	2	26	2	72	12	50	3	193

*Thirty-one people had more than one type of cardiovascular disease, for example, hypertensive was often combined with coronary arteriosclerotic heart disease.

TABLE V. NUMBER OF PERSONS IN CARDIAC STUDY WITH POTENTIAL OR POSSIBLE HEART DISEASE BY SEX, AGE, AND RACE

SEX	RACE	AGES					TOTAL NO.	PER CENT
		20-29	30-39	40-49	50-59	60-		
Men	White	5	5	9	19	9	47	3.0
	Negro	2	3	1	3	3	12	4.0
Total		7	8	10	22	12	59	3.2
*P. P. H. D.		2.6	1.7	2.2	4.8	5.6	3.2	
Women	White	4	4	4	2	4	18	5.1
	Negro	2	1	0	0	0	3	8.6
Total		6	5	4	2	4	21	5.3
*P. P. H. D.		6.3	5.4	3.7	2.6	22.2	5.3	
Total Men and Women		13	13	14	24	16	80	3.6
Percent *PPHD Men and Women		3.5	2.3	2.5	4.5	6.8	3.6	

*Per cent of Potential or Possible Heart Disease in each age group, sex, race in entire population of 2,252.

The physical examination alone was responsible for the diagnosis of all cases of rheumatic heart disease, and for 85 per cent of the cases diagnosed hypertensive heart disease. Only 8 per cent of the patients discovered to have coronary arteriosclerotic heart disease were diagnosed by physical examination. The physical examination alone was responsible for diagnosis of 57 per cent of all heart diseases detected in the survey.

Twelve or thirteen lead electrocardiography was abnormal in 65 per cent of all heart diseases. There were 13 per cent false-positives. This is discussed in detail later.

The value of the electrokymogram remains in doubt. The electrokymogram was interpreted as abnormal in only 14 per cent of persons with diagnosed heart disease.

Fluoroscopy revealed abnormalities in 50 per cent of the heart cases but did not contribute to the diagnosis of coronary arteriosclerotic heart disease.

The minifilm, as read by chest physicians in a routine manner, was of minimal value in the detection of heart disease; it was interpreted as suggestive of heart disease in only seven of the 162 cases, all of which were diagnosed by other techniques.

The history form, physical examination, electrocardiogram, and fluoroscopy contributed about equally to the diagnoses. The physical examination and fluoroscopy were also free from false-positives; however, these two techniques (physical examination and fluoroscopy performed by specialists) are not suitable for mass screening in the detection of heart disease. Furthermore, they are insensitive in the detection of coronary arteriosclerotic heart disease which is a frequent type of heart disease in the adult population. Therefore, it becomes necessary to evaluate critically other techniques of case finding such as a questionnaire history form and/or electrocardiography.

TABLE VI. DIAGNOSTIC METHODS WHICH CONTRIBUTED TO DISCOVERY OF CARDIAC ABNORMALITIES

ABNORMALITIES	NO. OF PERSONS	NUMBER AND PER CENT OF SPECIFIC CARDIAC ABNORMALITIES DISCOVERED BY VARIOUS DIAGNOSTIC METHODS											
		HISTORY		PHYSICAL EXAM.		ECG		EKG		FLUOR.		ROENT-GENOGRAM*	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Heart disease etiology hypertensive	95	49	52	81	85	61	64	14	15	64	67	5	5
Heart disease etiology coronary-arteriosclerotic	53	50	94	4	8	24	45	9	17	5	9	0	—
Heart disease etiology rheumatic	25	15	60	25	100	11	44	2	8	15	60	1	4
Heart disease etiology unknown	12	1	8	1	8	8	66	0	—	6	50	1	8
Heart disease etiology syphilis	4	3	—	3	—	3	—	1	—	4	—	0	—
Heart disease etiology congenital	2	2	—	1	—	1	—	0	—	0	—	0	—
Heart disease etiology cor pulmonale	1	1	—	1	—	1	—	0	—	1	—	0	—
Heart disease etiology other	1	1	—	1	—	1	—	0	—	0	—	0	—

*As read by Chest Physician.

Note: Percentages not calculated for less than ten people.

THE QUESTIONNAIRE HISTORY FORM

Of the individuals with heart disease, 62.5 per cent answered at least one of the first seven questions on the history form "positively." However, thirty-one of the subjects without heart disease also answered one or more questions "positively." The large number of apparently "false-positives" would make such a screening technique invalid. Analysis of the individual questions suggests that three of them, as a unit, are reasonably sensitive and specific. This raises the possibility that further experience with questionnaire histories may develop additional sensitive and specific questions.

The first question, "Can you walk a reasonable distance out of doors without trouble?" was insensitive. Only 7.5 per cent of cardiac patients and 1.3 per cent of presumably normal patients answered "No" to this question.

The second question, "Do you ever have distress, pain, or an uncomfortable feeling in the chest while walking on the street or up inclines or steps?" was answered "Yes" by 33.3 per cent of cardiac patients and by 4.5 per cent of apparently normal individuals.

Question 3, "While walking, are you forced to stop in order to rest?" was answered "Yes" by 20 per cent of cardiac patients and 2.8 per cent of normal individuals.

Question 4, "Have you noticed increasing or undue shortness of breath with exertion?" was answered "Yes" by 44 per cent of people with heart disease and by 17 per cent of normal individuals. The value of this question is minimized because of the number of false-positives. It is of interest that the percentage of positive answers to this question increases with age. Thirty-three per cent of all patients over 60 years of age, 27 per cent between 50 to 59 years, 19 per cent between 40 to 49 years, 12 per cent between 30 to 39 years, and 8 per cent between 20 to 29 years, answered "Yes." Comparing these figures with percentages of diagnosed heart disease (Table III), it is clear that the percentage of false-positive answers to Question 4 is highest in those over 39 years of age. Hence a history of increasing shortness of breath is more important as a screening device in younger age groups.

Question 5, "Is your sleep disturbed because of coughing spells, difficulty in breathing when lying flat, 'asthmatic attacks,' or choking sensation in the chest?" was insensitive and nonspecific. Only 6 per cent of patients with cardiovascular disease answered this question affirmatively.

Question 6, "Have you ever had palpitation of the heart?" was also of little value. Of the patients with heart disease 25.6 per cent and of the normal patients, 10.8 per cent, answered "Yes."

Question 7, "Are your ankles swollen at bedtime?" was of no value in this survey. Of the cardiac patients 8.8 per cent and of the normal patients 4.2 per cent answered "Yes."

Analysis of questions 2, 3, and 4, showed that as a group, 50 per cent of the individuals with heart disease answered one or more of these questions affirmatively while 18 per cent of the presumably normal individuals also gave a positive

answer. In summary, while the history form relative to symptoms of cardiovascular disease assisted in the diagnosis of 62.5 per cent of individuals with heart disease, 31 per cent of "normal" individuals (false-positives) would have been screened out in this survey as possible cardiacs. Questions 2, 3, and 4, as a group reduce the false-positives from 31 per cent to 18 per cent while reducing the true positives from 62.5 to 50 per cent.

THE ELECTROCARDIOGRAM

There were 410 electrocardiograms interpreted "abnormal." Sixty-five per cent of the individuals with heart disease and 13 per cent of the presumably normal people had abnormal electrocardiograms (Table VII). The 12 or 13 lead electrocardiogram was, therefore, more sensitive and more specific than history questions 2, 3, and 4, as a unit. The "minor" and "nonspecific" electrocardiographic abnormalities such as incomplete right bundle branch block, low voltage, slight prolongation of the P-R and QRS intervals were relatively equal in number in the groups with and without heart disease (Table VIII). Eliminating patients with the "minor" abnormalities would decrease the false-positive but also would significantly lower the sensitivity of the electrocardiogram in case finding.

TABLE VII. DISTRIBUTION OF ELECTROCARDIOGRAPHIC ABNORMALITIES IN PERSONS WITH AND WITHOUT HEART DISEASE

	CARDIAC DISEASE AND POSSIBLE AND POTENTIAL HEART DISEASE	NO CARDIAC CONDITION	TOTAL
Abnormal ECG	157	253	410
Normal ECG	85	1,757	1,842
Total	242	2,010	2,252

The three standard limb leads were sufficient for the diagnosis in 237 of the 410 abnormal electrocardiograms. Using the three standard limb leads alone, six "normal" electrocardiograms would have been interpreted as abnormal. Thus, using the three standard limb leads, the sensitivity of the electrocardiogram in case finding would have been reduced to 57 per cent. The unipolar limb leads aided in the definitive electrocardiographic diagnosis in only eleven cases. In sixty-five other cases, the unipolar limb leads supported the electrocardiographer's impression that a borderline Q_3 was of no significance.^{5,6} In the latter cases, a prominent S_1 was usually present and there was no abnormal Q_2 or S-T-T wave changes.

The unipolar precordial leads (V_1 to V_6 and V_{3R}) increase the sensitivity of the electrocardiogram in case finding to 65 per cent. This was a surprisingly small gain considering that the chest leads entail considerable effort and skill of the technician. Furthermore, multiple chest leads may be impractical in mass screening programs because it necessitates undressing. It should be emphasized

TABLE VIII. DISTRIBUTION OF "MINOR" ELECTROCARDIOGRAPHIC ABNORMALITIES IN SUBJECTS WITH HEART DISEASE AND IN SUBJECTS WITHOUT OTHER EVIDENCE OF HEART DISEASE

ECG DIAGNOSIS	HEART DISEASE	NO HEART DISEASE
Incomplete right bundle branch block	82	73
Low voltage QRS complexes	78	60
First degree heart block	42	34
With low voltage QRS complexes	1	1
With right bundle branch block	1	0
With intraventricular block	1	1
With incomplete right bundle branch block	4	3
With nondiagnostic S-T-T wave changes	1	0
Non-diagnostic S-T-T wave changes	30	23
Right bundle branch block	18	13
Intraventricular block	13	12
Abnormal arrhythmia	7	6
Slight prolonged P-R interval	0	1
"Borderline" left ventricular hypertrophy ($S-V_1 + R-V_5 = 35$ mm.)	0	1
Abnormal degree right axis deviation without changes of right ventricular hypertrophy or right bundle branch block (ADI equals - 15)	0	1
High voltage QRS complexes	0	1
Wolff-Parkinson-White syndrome	1	1
Second degree heart block	1	1
Abnormal degree left axis deviation without changes of left ventricular hypertrophy or left bundle branch block (ADI equals + 26)	0	1

* ADI = Axis deviation index.

that the unipolar limb leads and the precordial leads often were necessary for the definitive electrocardiographic diagnosis, but sufficient abnormalities were present in the standard limb leads to serve as a screening device in 57 per cent of the heart cases.

RELATION OF POSITIVE HISTORY TO ABNORMAL ELECTROCARDIOGRAM

The electrocardiogram and the history form did not detect the same type of cases. The electrocardiogram was most sensitive in detecting hypertensive heart disease, and the history form was best in detecting coronary arteriosclerotic heart disease. Three questions (items two, three, and four in the questionnaire history form) and the three standard limb leads of the electrocardiogram detected 92 per cent of all heart cases, but 35 per cent of normal individuals also either answered any one of the three questions affirmatively or had abnormalities in the three standard lead electrocardiogram.

SUMMARY AND CONCLUSIONS

Seven per cent of a sample civil service population at work were found to have diagnosable heart disease. The electrocardiogram is the best single technique in cardiac case finding. Of all heart cases in this survey, 65 per cent were found by using all 12 leads, and 57 per cent if only the three standard limb leads were taken. Of the presumably normal individuals, 13 per cent, would be erroneously suspected of possible heart disease by this technique. As a group, Questions 2, 3, and 4 of the history form detected 50 per cent of heart cases. Eighteen per cent of normal individuals would be suspected of possible heart disease by this case-finding device. Additional investigation is desirable to develop and evaluate suitable screening techniques for the detection of heart disease. A questionnaire history form may be a partial answer to this problem. Further experience is required to answer the difficult and delicate problem of effective cardiac case finding. Any technique with a high frequency of false-positives is not acceptable because of the great risk of inducing heart consciousness or iatrogenic heart disease, and because of the cost of follow-up examinations.

The examining physicians are Doctors Edward Phillips, Milton Glickman, Joe Golenternek, and Walter Graf. Dr. Milton Glickman assisted in the reading of the electrocardiograms. Mr. E. A. A. Schori and L. Reiser, M.P.H. gave valuable statistical advice throughout the study. Dr. Samuel A. Levine of Boston offered valuable suggestions regarding the history form and physical examination. The professional staffs of the Chronic Disease Bureau of the California State Department of Public Health and the National Heart Institute assisted in the development of all phases of this project.

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THE NATURAL HISTORY AND COURSE OF HYPERTENSION WITH PAPILLEDEMA (MALIGNANT HYPERTENSION)

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THE VARIABILITY and unpredictability of the clinical course of hypertensive vascular disease has been recognized for many years. One type, which is characterized by a rapid downhill course and can be recognized at the outset by the appearance of papilledema, has been singled out as particularly ominous. Differentiation between the benign and malignant phases of hypertension on the basis of the course of the disease was first made pathologically by Volhard and Fahr¹¹ and clinically by Janeway.¹² Early recognition of the malignant phase was clarified by Keith and Wagener,¹⁴ who, in 1928, demonstrated the relationship between changes in the optic fundi and in the prognosis of the patient.

A number of studies^{4,5,14,23,28,37} have described the various clinical and experimental aspects of malignant hypertension, but the etiology and pathogenesis of the malignant phase have not yet been established.

In the course of our studies on the natural history of hypertension, patients were encountered who, although apparently in good physical health, with satisfactory renal function and minimal symptoms, showed evidence of mild papilledema with or without the presence of hemorrhages and exudates. The question arose as to whether the prognosis was as ominous in these as in the patients with well-developed papilledema, hemorrhages and exudates, classified by Keith and Wagener¹⁴ as Group IV retinitis. The question arose particularly in reference to those patients in whom the optic discs were slightly blurred without clear-cut papilledema and in whom exudates or hemorrhages might be minimal.

The present study was therefore undertaken to determine the natural history of hypertension associated with papilledema, that is, "malignant" hypertension. We undertook to verify the serious prognostic significance of papilledema in hypertensive patients and to trace the progression of lesions in the affected body systems by means of history, physical examination, and laboratory studies.

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SUBJECTS AND METHODS

The patients in this series were seen at the University of California Hospital or Outpatient Department during the years 1936 through 1949. An effort was made to study all cases of malignant hypertension seen during this period. The cases were located by a survey of patients with the diagnoses of arteriolar nephrosclerosis, advanced stage, encephalopathy due to arterial hypertension, hypertensive vascular disease of intrinsic vessels of the retina, malignant hypertension or retinitis of hypertension, and in whom the retinae were classified as Keith-Wagener IV by known reliable observers. A total of 104 patients with malignant hypertension obtained in this manner comprise the basis for the data in this paper.

Sex: Our group consisted of 63 men and 41 women, roughly a 3:2 ratio in favor of men. This is in close agreement with the totals from previously published series.³⁷

Age: The average age at the time the diagnosis of malignant hypertension was established at our hospital was 42.9 years; in men it was 44.2, and in women 40.9 years. The range of ages extended from 13 to 71 years, with fifty-nine patients (57 per cent) falling between the ages of 30 and 50.

FAMILY HISTORY

The family histories recorded in the routine hospital records were reviewed in all cases. The following conditions were considered an indication of hypertensive vascular disease although possibly some were due to causes other than hypertension: known high blood pressure, cerebrovascular accidents, dropsy, heart attacks or heart trouble, Bright's disease, and sudden death from unknown cause. In the families of fifty-one of the patients, none of these conditions was known to have occurred; in the remaining fifty-three families, they occurred in at least one member. In the families of seventeen patients, both parents had an indicative condition; in twenty-two, only one parent. Five patients knew of more than three relatives with such conditions.

The incidence of a family history of hypertensive cardiovascular disease in half the group was higher than might have been expected from previous data. One-sixth of the patients in Klemperer and Otani's²³ group had a family history of hypertension, heart, or kidney trouble, and one-third in Page's²⁸ group. Of the entire population of the Hypertension Clinic of the University of California Outpatient Department, however, 55 per cent had a family history of such conditions.

PAST HISTORY

"Malignant" hypertension has been described as "striking like a bolt from the blue." Ellis⁵ found a long history of hypertension or its symptoms unusual in his group of 103 patients. In Keith and Wagener's¹⁴ group, however, 59 per cent had preceding hypertension of a duration of a few weeks to ten years. Derow and Altschule⁴ elicited a history of preceding hypertension in eleven out of fifteen patients, with an average duration of three years. Klemperer and Otani²³ recorded its presence in all but one of their sixteen patients.

In our group, thirty patients were unaware of the existence of hypertension before the onset of the malignant phase. In the remaining seventy-four (71 per cent) it had been found from 5 months to 27 years earlier.

Significant past illnesses were recorded for all patients, and an attempt to correlate reliability of the past history with diagnosis at post-mortem examination will be made later in this report. Thirty patients reported past episodes of scarlet fever or frequent, severe sore throat. Typical glomerulonephritis occurred in two patients, and symptoms suggesting an acute attack were mentioned by three others. Pyelonephritis was suspected from the history in eighteen patients, in six of whom calculi had occurred. Thirty-one of the forty-one women had pregnancies, and in twelve symptoms suggestive of toxemia had occurred (hypertension, albuminuria, generalized edema, excessive weight gain, severe headaches, convulsions, or visual disturbances). In one patient the toxemia of pregnancy appeared to develop directly into malignant hypertension:

Patient 69 was seen at the University of California Hospital at the age of 37 years. She had had her first uncomplicated pregnancy at the age of 20. At 25, with her second pregnancy, the systolic blood pressure rose to 175 mm. Hg after the fifth month. At the age of 34, in her third pregnancy, she developed a toxemia, with a systolic pressure of 200 mm. Hg, albuminuria, nausea, and vomiting during the seventh month. At the age of 37 years, just prior to being seen in our clinic, she again became pregnant and almost at once suffered dizziness, headaches, and blurred vision. The blood pressure was 240-280/130-170 mm. Hg. The fundi revealed papilledema, but the renal function was satisfactory. She died approximately eight months later of renal insufficiency.

Other probably coincidental illnesses which occurred in our group included syphilis in three patients, chronic bacterial infections (tuberculosis and chronic osteomyelitis) in five, diabetes in three, and adenocarcinoma of the sigmoid colon in one. The low incidence of syphilis is interesting, since Fahr attributed such importance to it in the etiology of malignant hypertension.

DURATION OF ILLNESS

In an effort to determine the actual duration of the syndrome of malignant hypertension, we estimated the date of onset from the history. The symptoms considered to mark the beginning of the malignant phase were: disturbed vision, when of acute onset or of sufficient severity to constitute a chief complaint, since we had accepted the requirement of Keith-Wagener IV eyegrounds in making the diagnosis of malignant hypertension; and gross hematuria, when, as far as could be ascertained clinically or at post-mortem examination, it represented "renal epistaxis" (when blurred vision and hematuria appeared almost simultaneously, the first to occur was chosen). In the absence of these symptoms, clear-cut, sudden severe headaches, especially if associated with nausea and vomiting, were regarded as the indicative sign. When headache occurred before either disturbed vision or hematuria, it was considered prodromal, unless a retinal classification of Keith-Wagener IV at the time verified the presence of malignant hypertension. When none of these symptoms occurred, any acute episode which seemed to precipitate the illness was recorded.

The following case demonstrates onset of hypertension by almost simultaneous hematuria and visual loss:

Patient 100, a 47-year-old man, had developed transient elevation of the blood pressure after an automobile accident ten years earlier. Hypertension was found on physical examination at the age of 44. In April, 1949, just prior to admission, he developed paroxysmal nocturnal dyspnea. At this time his retinæ revealed hemorrhages and exudate, but no papilledema. A month later, on May 4, he passed grossly bloody urine; on May 8 he first noted blurring of vision, which progressed rapidly to the point at which he was able to discern only gross outlines. At this time he was found to have three-diopter elevation of his discs. The patient died a week later.

From the date of onset, determined as described above, and the date of death, it was possible to estimate the duration of the malignant phase. In the seventy-seven patients in whom the exact date of death was known, the average survival was 8.7 months, with a range of two weeks to six and one-half years and a median of five months.

Because this involved a subjective estimation of onset from the patient's history, we checked our accuracy by using the date when the diagnosis of malignant hypertension was established by the presence of a Keith-Wagener IV retinitis. The average survival in eighty-six patients (excluding those still living) was 8.4 months. The range was from one day to seven years, with only six patients living more than two years and fifty (almost half) dying within three months after the first diagnosis of Keith-Wagener IV retinitis.

These figures agree closely with those of Keith and Wagener,¹⁴ who found an average survival of eight months after the recognition of papilledema. Derow and Altschule⁴ found the average duration of the malignant phase in their patients was five months, while Ellis⁵ stated that almost all of his group died within one year after developing papilledema.

Four of the 104 patients in our group have survived longer than five years after a retinal examination first revealed a Keith-Wagener IV classification; three of the four received no definitive therapy. Case reports on the four patients follow:

Patient 43, a divorced woman, 44 years old, was found to have a blood pressure of 184/130 mm. Hg when seen in the University of California Outpatient Department in 1936. She had scarlet fever at the age of 25 years and pyelonephritis during a pregnancy at the age of 29 years. The examination was negative except for slight left ventricular hypertrophy; the renal function was satisfactory. Four years later, the situation was unchanged except for more definite left ventricular hypertrophy. She then developed severe headache, and in July, 1941, she noted the onset of scotoma. The retinæ of her eyes showed slight edema of both discs, one cotton-wool patch, a few punctate hemorrhages, and severe narrowing and sclerosis of the arterioles. Symptomatic therapy was given, and the retinal changes of edema, exudate and hemorrhages disappeared. The situation remained unchanged until February, 1946, when she developed a mild right hemiplegia. At this time, her renal function was moderately impaired, and the retinæ again showed papilledema, hemorrhages and exudate. She died suddenly in December, 1947, of a dissecting aortic aneurysm. The papilledema was still present at that time.

Patient 59, a married woman, 50 years old, was seen at the University of California Outpatient Department in June, 1941, because a routine examination revealed a systolic blood pressure of 210 mm. Hg. She had had mild dyspnea for a year and gradual decrease in visual acuity over a period of three years, and on questioning she complained of fatigability during the preceding six weeks. Retinal examination showed the disc of the right eye to be normal, while the left was elevated three diopters. The vessels of the eye showed severe narrowing, spasm and sclerosis. There were many small hemorrhages and cotton-wool patches. She had moderate left ventricular hypertrophy and satisfactory renal function, with a specific gravity of 1.022 on a casual specimen. She was not seen again until seven years later, when she was hospitalized because of acute myocardial infarction, from which she died. Papilledema was not present at this time.

Patient 65, a 52-year-old married man, immigrant from Greece, was seen in the University of California Outpatient Department in April, 1943, with a chief complaint of blurred vision for two years. No other significant symptoms had occurred. His eyegrounds showed mild edema of the left disc, a flat right disc, moderate spasm and sclerosis of the arterioles, punctate and flame hemorrhages and exudates. His heart was moderately enlarged, and his blood pressure was 180/110 mm. Hg. Renal function was satisfactory, with a specific gravity of 1.026 on a casual specimen. He was not seen again until July, 1948, at which time he had a hemiplegia. He died two years later of a cerebrovascular accident.

Patient 73, a 39-year-old married man, electrical engineer, was found to have hypertension in November, 1939, when he consulted a physician because of headaches, fatigue, and loss of weight. Five months later, he developed blurring of vision which became so severe that he was unable to recognize members of his family. Retinal examination revealed one-diopter elevation of the discs, narrowed and sclerotic arterioles, a few hemorrhages and a macular "star." His blood pressure ranged from 275-245/130-120 mm. Hg. There were no cardiac abnormalities. Urinalysis showed a specific gravity of 1.025. Intravenous pyelograms revealed a small nonfunctioning left kidney and a normal right kidney. A left nephrectomy was performed, and his blood pressure returned to normal by the twentieth postoperative day, at which time the papilledema had disappeared. He was last seen in July, 1950, when he was in excellent health, without cardiac, renal, cerebral, or visual symptoms or signs. This case will be reported in more detail in a subsequent paper.

These four cases, in our opinion, represented remissions in the course of malignant hypertension. Two of the patients had edema of only one disc, while only four patients in the entire group had unilateral papilledema. Of these, three were still living, one, twelve months, one, eighteen months after diagnosis of Keith-Wagener IV eyegrounds by retinal examination, and one had died two months after diagnosis. This gives an incidence of unilateral papilledema of 50 per cent in the group with remissions, as opposed to 3.8 per cent in the entire group; even though the number of cases is small, this may indicate a somewhat more hopeful prognosis in the presence of unilateral papilledema.

None of these four patients showed more than minimal renal impairment, and the course in the first three patients resembled that of benign hypertensive cardiovascular disease.

The remission in the last patient was presumably due to nephrectomy, and although minimal, transient elevation of blood pressure persisted, the course, which had been characteristic of malignant hypertension, was strikingly altered by the operation. A few cases of malignant hypertension with such dramatic results from nephrectomy have been reported in the literature, although, in general, the follow-up was shorter than in this patient.^{*20,24,30,32,36,51}

COMMENT.—We have found that the average survival in patients with malignant hypertension is about eight and one-half months. The survival in our group ranged from one day to eleven years after onset of the illness, with two-thirds of the patients dying within nine months. Only three patients, untreated, lived more than two and one-half years and all of these survived more than five years. These patients were considered to have had remissions. The onset of the malignant phase was marked by blurring of vision in three-fourths of our cases, while gross hematuria was the first symptom in roughly 8 per cent. The occurrence of either of these symptoms in a hypertensive patient should be regarded as serious.

*A second patient, seen since the completion of this paper, had a reversal of papilledema following nephrectomy for unilateral atrophic pyelonephritis.

PRODROMAL SYMPTOMS

With the hope of determining whether the onset of the malignant phase could be predicted, the presence of any symptoms or events prior to those clearly marking the onset of the malignant phase was determined (Table I). This is to be contrasted with the symptoms occurring at the onset of papilledema (Table II).

TABLE I. PRESENCE OF PRODROMES PRECEDING ONSET OF MALIGNANT PHASE IN 104 CASES

I. Symptoms simultaneous with onset.....	26
(All With Sudden Onset)	
Visual loss*	18
Acute headache	3
No symptoms	3
Gross hematuria*	2
II. Symptoms less than 6 months before onset.....	35
(Sudden Onset in 19)	
Headache	23
Weakness, malaise, fatigue	8
Congestive failure	7
Gastrointestinal symptoms	5
Weight loss	1
Loss of consciousness	2
Acute infections	5
Trauma to the head	1
III. Symptoms 6 months to 5 years before onset.....	43
(Sudden Onset in 5)	
Headache	26
Weakness, malaise, fatigue	9
Congestive failure	8
Gastrointestinal symptoms	6
Gradually failing vision	4
Dizziness	6

*Associated with headache and malaise in most.

TABLE II. SYMPTOMS MARKING ONSET OF MALIGNANT PHASE IN 104 CASES

SYMPTOM	NUMBER OF CASES
Visual impairment	79
Acute headache	6
Gross hematuria	5
Visual impairment and gross hematuria	3
Acute cardiac failure	1
Gastrointestinal upset with nausea, vomiting and epigastric pain	1
Undetermined due to vagueness of symptoms	9

It is seen that whether the onset was sudden, gradual, or obscure, the initiating symptoms were quite similar. Headache, congestive failure, gastroin-

testinal symptoms, and the "fatigue complex" occurred in about equal proportions. Nineteen of the thirty-five patients who developed malignant hypertension within six months were able to date the onset of the symptoms precisely, as could all patients with acute hypertension, whereas only five of the forty-three patients in the group in which the onset was obscure could do this. In the patients in whom the malignant phase developed within six months of the first symptoms, the symptoms were most often described as severe from the start, whereas in the other patients they were often mild at first but gradually increased in severity. It appears that the more sudden and severe the onset of symptoms, regardless of what these are, the more likely is there a rapid progression into the malignant phase.

CHIEF COMPLAINTS

Multiple major complaints occurred in most cases, but headache (forty-six patients), blurred vision (thirty-five patients), and "hypertension" (twenty-three patients) were the most common presenting complaints. Shortness of breath, fatigue, weakness, or malaise, and gastrointestinal symptoms were common complaints. Less frequently, urinary symptoms, hematuria, edema, cough, and pain in the chest were prominent.

THE RETINA IN MALIGNANT HYPERTENSION

The significance of retinal changes in hypertension has been repeatedly emphasized by Keith and Wagener.¹⁴ In 1939, they published an excellent study with a review of the literature on the etiology of hypertension and the accompanying retinitis, and their classification of retinal changes into Groups I through IV has been used in our study.

In the present series of 104 patients, visual symptoms were among the chief complaints in thirty-five patients, being second in frequency to headaches. They were considered to have marked the onset of the malignant phase in eighty-two patients, although during the course of the disease, ninety-four patients (90 per cent) reported visual changes.

The retinal changes ranged from gradually decreasing visual acuity to sudden blindness; the most frequent was "blurring" (sixty patients). Twenty-one patients complained of "failing," "poor," or "dim" vision, while marked loss occurred in eight and blindness in eleven. The onset of visual symptoms was usually fairly sudden; most patients could give accurate dates for its occurrence. Only twenty-two reported gradual changes. Less frequent changes included homonymous hemianopsia, loss of one temporal field and loss of one quadrant, each occurring in one patient. Six patients noted scotomata and two, diplopia.

Objective findings are tabulated in Table III. By definition, the retinae of all patients were classified as Keith-Wagener IV at some time during the course of the disease. Hemorrhages and exudates were almost uniformly present. In eight patients, the retinae showed elevated discs and exudate, but no hemorrhage. Of these six had edema, exudates or macular "stars" only. In one patient, the retinae showed elevated discs and moderately advanced vascular changes; hemorrhage or exudate did not occur until three months later. Unilateral papilledema was noted in six patients, two of whom survived more than five years, one died two months after diagnosis and the other three were still living one, two, and eighteen months after diagnosis. Blurring, but no measurable elevation of the discs, was reported in eleven patients whose retinae also revealed hemorrhages, exudates and vascular changes. Lumbar punctures were performed on five of these eleven patients; in two the spinal fluid pressure was elevated.

TABLE III. RETINAL CHANGES IN 104 PATIENTS WITH MALIGNANT HYPERTENSION

Papilledema	104
Unilateral	6
Vascular changes	104
(localized and generalized narrowing, sclerosis)	
Exudates	104
(one patient was seen with papilledema without exudate until three months later)	
Hemorrhages	96

In our series only three of the patients who complained of visual disturbances failed to show papilledema. Two of the three patients apparently had episodes of papilledema preceding the visual loss, which had subsided by the time retinal examinations were made. The third patient may have had a central cerebral lesion, since the visual loss was homonymous hemianopsia.

In seventeen patients, changes classified as Keith-Wagener IV were noted before the onset of visual symptoms. In seven of the patients, the symptoms appeared an average of twelve weeks after the examination, with a range of from five days to nine months. The remaining ten patients did not develop visual symptoms while under our observation. Two of the ten patients were seen only briefly, during an early period of their illness. Two other patients were followed for as long as two and one-half years; in both, papilledema persisted for only a short time. The average period of follow-up for the group was ten months.

Progression of retinal abnormalities to include papilledema occurred in twenty-six patients while under our observation. The remainder of the group had Keith-Wagener IV retinæ when first seen. Of the twenty-six patients who showed progressive retinal changes, ten were observed from the time when the fundi showed minimal or no changes. The average time in which the changes progressed to the Keith-Wagener IV stage was thirty-eight months; the shortest interval was seven to eight months. The nine patients whose retinal changes were observed to progress from Keith-Wagener II to IV did so in an average of twenty months. The range was from three weeks to five years. Nine others demonstrated the shift from Keith-Wagener III to IV in their retinæ. This occurred in an average of eleven months, with a range of from three weeks to thirty months.

Disappearance of papilledema.—Regression under observation, including disappearance of papilledema, occurred in only three patients whose improvement occurred without specific therapy. All patients who have received treatment with a rice or low sodium diet, sympathectomy, nephrectomy, or hexamethonium have not been included here but will be considered in a later paper. These three patients have already been described (Patients 43, 59, and 65). None of these three patients died of renal insufficiency. One died of a dissecting aortic aneurysm, one of myocardial infarction, and one of a cerebrovascular accident.

SUMMARY.—The visual symptoms and retinal changes in a group of 104 patients with malignant hypertension have been reviewed. Ninety per cent of the group complained of impairment of vision during the course of the illness, and in almost all, this symptom was considered to mark the onset of the malignant phase. Papilledema, vascular changes, and exudate were present in all patients at some time during the course of the disease; hemorrhages were seen in all but eight patients. There was a close correlation between loss of vision and the appearance of Keith-Wagener IV retinitis. Twenty-six patients were observed before the retinitis progressed to a Keith-Wagener IV classification. The

average interval before the appearance of papilledema depended upon the severity of the fundal changes on the initial examination; the more severe the initial findings, the shorter the interval. Regression of retinitis was observed in only three patients who did not receive some vigorous form of surgical or dietary therapy, and these three patients survived over five years. The retinae appear to be singularly effective as mirrors reflecting the course of hypertensive disease.

THE HEART IN MALIGNANT HYPERTENSION

The heart is one of the most vulnerable organs in hypertensive disease. Hypertrophy of the left ventricle, which may be asymptomatic for years, is usually the earliest clinically recognizable change and may result in disproportion between muscle mass and blood supply. Development of coronary atherosclerosis, another frequent occurrence, increases this disproportion. Myocardial insufficiency, infarction, and arrhythmias may be observed in later stages. Of 1,264 hypertensive patients from various series collected by Goldring and Chasis,⁸ 66 per cent died from heart disease. In about 53 per cent of the patients, death was due to congestive failure; in the remaining patients, it was caused by coronary thrombosis.

Similar or more severe cardiac changes may be expected in the course of malignant hypertension.^{14,28,44} In our 104 patients, all information relative to the heart was tabulated (Table IV).

TABLE IV. CARDIAC FINDINGS IN 104 PATIENTS WITH MALIGNANT HYPERTENSION

Cardiac enlargement (slight or moderate in 67; marked in 14)		
Clinically		81
Radiologically		57
Symptoms of cardiac failure or decreased cardiac reserve		73
Signs of cardiac failure		51
Observed before onset of malignant phase	8	
Observed simultaneously with onset of malignant phase	11	
Developed during first year of illness	28	
Developed during second year of illness	4	
Angina pectoris		20
Murmurs (systolic, except for 5 diastolic)		72
Gallop rhythm		30
Pericardial friction rub		10
Pulsus alternans		9
Arrhythmia		5
Electrocardiographic abnormalities (of 89 patients)		82
Left ventricular hypertrophy:		
"characteristic of" or "probably"	48	
"suggestive of"	14	
Myocardial changes secondary to coronary disease	15	
No characteristic pattern	13	
Within normal limits	7	

The relation of the onset of cardiac failure to the onset of malignant hypertension was of interest. Of the seventy-three patients who had symptoms of cardiac failure, in eleven, these symptoms developed simultaneously with the onset of the malignant phase; and in twenty-one

within a year after its onset. Twenty patients noted onset of symptoms of cardiac insufficiency during the year preceding the beginning of the malignant phase, while twenty others developed symptoms from four to five years before. In twelve of the forty who developed symptoms before the onset, no objective changes were noted at any time. Thus, forty (38 per cent) of the group had symptoms of cardiac disability well before the onset of malignant hypertension. In nine patients, no signs of failure occurred at any time.

A summary of the cardiac changes found at autopsy in our patients follows: Data on the heart were available in twenty-five patients. The heart weight in adults ranged from 360 to 800 grams, with an average weight of 527 grams, slightly less than the average range of 550 to 600 grams found by previous investigators. The heart of a 13-year-old girl in our group weighed 320 grams. The left ventricle in adults averaged 22.7 mm. in thickness, with a range of from 17 to 30 millimeters. The right ventricle averaged 5.5 mm., with a range of from 3 to 10 mm. in thickness.

Pericarditis was found in eight patients, of whom seven were in uremia. The eighth patient died suddenly after a lumbar puncture and was found to have chronic adhesive pericarditis.

The coronary arteries usually revealed mild or moderate atherosclerosis. In three patients they were reported to be normal. These patients were: No. 22 was a 34-year-old woman with hypertension of two years' duration and a malignant phase of two months' duration. The electrocardiographic pattern was of left ventricular hypertrophy; weight of the heart was 360 grams. No. 29 was a 31-year-old woman who had Cushing's disease during the preceding five years which terminated rapidly in malignant hypertension. Electrocardiograms had shown no characteristic pattern; her heart weighed 540 grams. No. 60 was a 16-year-old girl who had chronic glomerulonephritis. The electrocardiographic pattern was suggestive of left ventricular hypertrophy; the heart weighed 400 grams.

COMMENT.—In summary, four-fifths of our group had symptoms referable to the cardiovascular system at some time during the course of the disease. Three-fourths had symptoms suggestive of decompensation, while one-half had signs confirming its presence. In roughly two-fifths of these patients, the symptoms developed before the onset of malignant hypertension, and in one-fifth, signs of failure occurred before the malignant phase. The average duration of hypertension in the group who developed failure was significantly longer than in the group who did not. Angina pectoris occurred in one-fifth of the group, but arrhythmias were found in only one-twentieth. All patients who developed gallop rhythm or pulsus alternans died in less than a year; the average survival was about two months. In the patients in whom the size of the heart was determined by roentgenogram examination, enlargement was found in 75 per cent. Over 90 per cent of the patients on whom electrocardiograms were taken had abnormal records; 70 per cent showed patterns suggestive of left ventricular hypertrophy, and 17 per cent showed changes probably secondary to coronary artery disease. All patients who came to autopsy were found to have enlarged hearts; the average weight of the heart in adults was 527 grams. From these observations it appears that the heart is almost universally affected during the course of malignant hypertension.

THE CENTRAL NERVOUS SYSTEM IN MALIGNANT HYPERTENSION

Another territory of well-recognized vulnerability in hypertensive disease is the central nervous system.^{8,23,31} Transient episodes of vasoconstriction, thromboses and hemorrhages are indicative of varying degrees of vascular damage in this area. Cerebrovascular accidents account for approximately 15 per cent of

the deaths of patients with hypertension. Rosenberg³⁵ carefully studied the brains of seventeen patients dying of malignant hypertension and found destructive lesions in twelve (71 per cent). He noted that the walls of the cerebral arterioles were greatly thickened, so that the caliber of the lumen was narrowed. The lesions responsible for various types of symptoms included multiple miliary hemorrhages or infarcts, large, destructive vascular lesions, and intra- or extra-cerebral edema. In five of the seven patients on whom lumbar punctures were performed, the cerebrospinal fluid pressure was elevated. Kessler and associates²² regarded increased intracranial pressure as secondary to a sustained increase in venous pressure and an increase in permeability of the hemato-encephalitic barrier, most likely due to capillary sclerosis. In a study of fifty patients who had marked hypertensive disease but who were not in advanced congestive failure, Shelburne and associates³⁸ found twenty-one with increased intracranial pressure. Headaches and papilledema have been regarded as the characteristic clinical signs of cerebrospinal hypertension, although it has been recognized that both may occur in its absence. Indeed, recent work has indicated that high intracranial pressure alone may not be sufficient to cause headache; pain results only when there is traction upon some sensitive structure.

Wolff⁵⁰ described the headache characteristically associated with hypertension as dull, diffuse, and aching, although usually at the outset it is throbbing. It may be generalized, unilateral, or occipital, and occurs most commonly in the early morning hours. It is not related in frequency or severity to the height of the blood pressure. He presented evidence to show that these headaches arise, like migraine, from dilatation and distention of the branches of the external carotid artery. The headaches may be relieved by ergotamine tartrate or by manual compression or ligation of the arteries involved. They are not influenced by changes in intracranial pressure. On the other hand, headaches associated with renal failure in addition to hypertension apparently increase in severity when the cerebrospinal fluid pressure increases, although they are not abolished by diminishing the pressure. It has been suggested that local edema of the brain producing traction upon the great venous sinuses is the causative mechanism. This theory is supported by the fact that on occasion intravenous injections of 50 per cent glucose may dramatically relieve the pain, presumably by its dehydrating effect upon the brain. The headaches associated with sustained contraction of the skeletal muscles of the head also occur with some frequency in hypertensive patients. They are described as "viselike" or "cramping" and are associated with tenderness over the involved muscles.

The records of our group of 104 patients were checked for evidences of central nervous system involvement, and the following information was obtained:

Headaches occurred in ninety-one patients and were second in frequency only to the visual changes noted in ninety-four patients. In forty-six patients, headaches constituted part of the chief complaint, while in twelve they led to the discovery of hypertension. In twenty-two of the ninety-one patients, the headaches occurred simultaneously with the development of the malignant phase. The headaches began after the onset of the illness in only three patients. In twenty-three patients, headache was noted within a six-month period before the start of malignant hypertension; in this group it could be considered truly prodromal. In the remaining patients, headaches had been present over a longer period, although in a few individuals an increase in their severity and frequency was noted at the approach of the malignant phase.

The headaches occurred predominantly in the occipital and frontal areas, or both. Out of seventy-nine cases where the location was stated, twenty-three were occipital, twenty-one frontal, and sixteen combined fronto-occipital headaches. In twelve other cases, the headache was in a parietal or temporal region; in seven the pain was diffuse. In twenty-five of forty-two cases, the headaches were described as throbbing, while in eleven they were considered dull. They were almost uniformly described as severe in intensity, and in twenty of the twenty-five cases where stated, they occurred most frequently in the morning. The duration and frequency of the headaches were not described in adequate detail. The duration, however, ranged from about one hour to more than one week, and the frequency was stated most often as "occasional" or "every two to three weeks." The possible relationship of the occurrence of headaches to emotional stress was touched upon in only a few of the more recent cases.

Mental disturbances occurred in a number of patients. Six patients without uremia were described as generally slow in thought and speech and of poor memory. Stupor was noted in twenty-two cases; this figure is misleading, however, since reports on the terminal phase of the disease were often inadequate. Twenty-one patients were disoriented at some time during the course of the disease; no doubt the number would have been higher if full information had been obtainable on all patients. Among the factors held responsible for disorientation of the patient were uremia (13 patients), cerebrovascular changes (4 patients), and drug toxicity (2 patients). In two patients, psychotic episodes were responsible.

Evidence of gross cerebrovascular disturbances was found in forty-four patients. Of these, twenty-five had strokes; thirteen died, and twelve were left with changes ranging from obvious hemiplegia to minor motor and/or reflex abnormalities. This group also included six patients who reported prolonged episodes of unconsciousness, aphasia, facial palsy or other motor weakness, but who had no confirmatory neurological changes. Five additional patients reported only paresthesias, such as numbness of one limb or of one side of the body, which lasted for several days. Incoordination, manifested by staggering gait, dysarthria, or positive reaction to a Romberg test, was found in eight patients.

At the time of diagnosis of malignant hypertension, the average age in patients who manifested cerebrovascular disturbances did not vary significantly from the over-all average of 42.8 years. The average age for the entire group of forty-three patients was 41.9 years, and for the twenty-four patients with verified cerebrovascular accidents, 41.8 years. The known duration of hypertension was also approximately the same. In the total group, the duration was 5.7 years; in the forty-three patients with manifestations of cerebrovascular accidents, 5.0 years.

Of the twenty-five patients with verified cerebrovascular accidents, twenty-two had headaches. In ten, the headaches developed during the prodromal period or at the time of onset of the malignant phase, while in twelve, they had persisted over a period of years. The headaches of these patients were similar to those of the group at large. In only one of our group did typical Pel's crises precede a cerebral thrombosis or hemorrhage. This patient (No. 52) was a 27-year-old man who developed intermittent episodes of unilateral numbness on the right side two months before he suffered right hemiplegia.

Convulsions were reported in eighteen patients. In twelve, they occurred while the patients were dying in uremia, in all but one patient within the last week of life. The exception was No. 80, a 23-year-old woman who lived 6 weeks in a semistuporous state following a convulsive seizure. In three others, the nonprotein nitrogen was elevated at the time the convulsions occurred, but the patients were not in a terminal state.

Lumbar punctures were done on fourteen of the patients who had convulsions. Ten of these patients had cerebrospinal hypertension (exceeding 200 mm. of water), with pressures extending as high as 480 mm. of water; four patients had pressures within normal limits. Thus, in the group of patients with convulsions, the ratio of patients with elevated spinal fluid pressures to those with normal pressures was 5:2. In the entire group, the ratio was 5:3, not a significant difference.

Lumbar punctures were performed on a total of forty-eight patients. In twenty-one patients, two or more punctures were done, bringing the total number to 114. In thirty patients (62 per cent), the initial pressure was over 200 mm. of water on the first test, while in eighteen the pressure was normal. The distribution is shown in Table V.

TABLE V. LUMBAR PUNCTURES PERFORMED ON 48 PATIENTS WITH MALIGNANT HYPERTENSION

PRESSURE	NUMBER OF PATIENTS
Above 500 mm. H ₂ O	2
400-499	3
300-399	12
200-299	13
Total	30
100-199	16
Under 100	2
Total	18

The average duration of the malignant phase in patients in whom the spinal fluid pressure was elevated on initial lumbar puncture was 7.7 months, while in those in whom the pressure was normal, the average was nine months.

Because opinion differs as to the value of lumbar punctures as a therapeutic measure, an effort was made to assess their effect in our cases. This data is from an unpublished study by Kerr and Crohn²¹ at this hospital. Criteria of improvement were relief of headache, dizziness, lethargy or vomiting, better vision, and slower and more regular respirations. In twenty-one of the group, no indication of the effect of lumbar punctures was recorded, while in eleven cases it was stated that no changes in clinical status occurred. Improvement was noted in fourteen patients; subsequent punctures had an unfavorable effect on three of these patients. Lumbar punctures produced adverse effects in six other patients; severe headaches in one, sudden blindness in one, and coma in four. One of these last patients (No. 36) became comatose two hours after the removal of spinal fluid, which reduced the fluid pressure from 270 to 90 mm. of water. A second lumbar puncture at this time showed grossly bloody spinal fluid at a pressure of 140 mm. of water. The patient died an hour later, and the autopsy showed herniation of the right cerebellar tonsil through the foramen magnum, a spontaneous hemorrhage into the left lobe of the cerebellum, and acute recurrent glomerulonephritis.

Repeated punctures were often unsuccessful in lowering the cerebrospinal fluid pressure. Lumbar punctures were performed in rapid succession in eighteen patients. In six patients, the pressure rose on successive taps; in three it first rose, then fell below the level of the first tap; in nine the pressure was lowered. In six of the twelve patients in whom the pressure was decreased, the final pressure remained above 200 mm. of water. Repeated lumbar punctures brought the spinal fluid pressure down to normal in only six patients; they caused an increase in pressure in an equal number.

An estimate of the clinical effectiveness of lumbar punctures is as follows: No change in 66 per cent of patients; improvement in 22 per cent; adverse effects in 12 per cent.

Elevation of the protein level of the spinal fluid was slightly more frequent than increase in spinal fluid pressure. Twenty-eight determinations were made in twenty-three patients. In sixteen (69 per cent) of the patients, the protein levels were above 60 mg. per cent, while in seven the levels were normal. The range varied from 11 mg. per cent to 307 mg. per cent. Determination of both pressure and protein levels was made in twenty patients; in three patients both were normal, and in four both were elevated. In ten patients, the protein level was elevated, while the spinal fluid pressure was normal; in three patients the pressure was elevated and the protein level normal. Convulsions did not occur in patients whose protein levels and spinal fluid pressures both were normal.

SUMMARY.—In conclusion, headaches occurred in 88 per cent of our patients, but neither in characteristics nor in timing could they be considered definitive

of malignant hypertension. Their description corresponded most closely to the migrainelike type of hypertensive headache. About one-half the group suffered from headache well before the onset of malignant hypertension. Disorientation in twenty-one patients and psychoses in two gave more direct evidence of functional central nervous system involvement. Cerebrovascular disturbances were manifested in forty-four patients (42 per cent), of whom twenty-five had strokes. This group of patients did not differ from those of the entire group in age, duration of hypertension, or type of headache. Convulsions occurred in eighteen patients, two-thirds of whom were in terminal uremia. Lumbar punctures showed elevated cerebrospinal fluid pressure in 70 per cent of the group with convulsions. Of the forty-nine patients on whom lumbar punctures were performed, 62.5 per cent had elevated pressures, which ranged as high as 500 mm. of water. The therapeutic effectiveness of lumbar punctures was estimated as beneficial in 22 per cent of the group, ineffective in 66 per cent and harmful in 12 per cent. Repeated taps to lower the pressure to normal were successful in one-third of the patients, while in an equal number the pressure rose further. The protein level of the spinal fluid determined in twenty-three patients was elevated in sixteen (69 per cent). The highest level was 307 mg. per cent. In ten patients, the protein level was elevated in the presence of normal pressure.

A discussion of the central nervous system and malignant hypertension would be incomplete without reference to the role of the emotions and possible psychogenic factors in etiology (Wolf and associates,⁴⁹ Gressel and associates¹⁰). Reiser and associates³⁴ found a close relation between emotional tension and the diffuse arteriolar spasm of hypertension. In twelve patients with papilledema, they found that the severity of the clinical manifestations of hypertension were in part related to the intensity of the emotional conflict. The data in our present series of cases does not permit detailed analysis with respect to this question, although in a few of our patients, significant emotional events preceded in time the onset of the malignant phase. In the past four years, a psychiatric appraisal of all patients with malignant hypertension has been made (Hunt and Sokolow¹¹), and in general, our results tend to confirm the observations of Reiser and associates.³⁴

THE BLOOD PRESSURE IN MALIGNANT HYPERTENSION

Severe hypertension is accepted as one of the criteria for the diagnosis of malignant hypertension. The range of maximum readings in Keith and Waggener's¹⁴ series was 220-280/120-190 mm. Hg. Page²⁸ and Ellis⁵ agreed that the diastolic pressure was rarely under 130 mm. Hg.

The highest and lowest readings for each of our patients were recorded. The range of the highest pressures was 300-160/180-110 mm. Hg, with an average of 248/150 mm. Hg. The lowest pressures ranged from 265-90/150-60 mm. Hg, and averaged 190/117 mm. Hg. Diastolic pressures below 80 mm. Hg occurred in several patients during episodes of spontaneous fainting or during the terminal period of the disease. Since the average of the lowest readings was 190/117 mm. Hg, it might be more accurate to regard 120 mm. Hg as the level below which the diastolic pressure rarely falls without good reason.

THE KIDNEY IN MALIGNANT HYPERTENSION

The kidney, historically and clinically, is the most important organ involved in malignant hypertension. Recognition of the significance of the pathologic renal changes, by Volhard and Fahr⁴³ in 1914, resulted in the segregation of malignant nephrosclerosis as a distinct entity in hypertensive disease. Recent work has indicated that the kidney may not only be overtaken by the changes of malignant nephrosclerosis but also may be the site of origin of secondary hypertension, upon which the syndrome of malignant hypertension is superimposed. It is apparent that changes seen clinically will be influenced by this fact.

In our group, 84 per cent reported symptoms related to the genitourinary system, either in their past histories or during the course of their illness. Most significant of these was gross hematuria. It will be recalled that hematuria was one of the symptoms used to mark the onset of the malignant phase when no more definite signs, such as renal calculi, were evident. In ten of our patients, hematuria occurred at the beginning of the malignant phase, while in seventeen others it developed during the course of the illness, giving a total of twenty-seven patients (26 per cent) who manifested this symptom during the malignant phase. Autopsies in these patients revealed nephrosclerosis in seven, glomerulonephritis in five and pyelonephritis in only one. Gross hematuria occurred in 70 per cent of the patients known to have had glomerulonephritis, and in 50 per cent of those known to have had nephrosclerosis, but in only one of the twelve patients with known pyelonephritis. This patient had a staghorn calculus which may have caused the hematuria. Five additional patients had episodes of hematuria in early life; renal calculi were demonstrated and were held responsible in three. One patient gave a characteristic history of glomerulonephritis in childhood and the other was believed to represent a case of march hemoglobinuria. Thus, one-fourth of our group had gross hematuria during the course of malignant hypertension; in these patients, glomerulonephritis or nephrosclerosis was the predominant basic renal lesion.

The most frequent genitourinary complaint was nocturia, which occurred in seventy-four cases. In 60 per cent of the patients, it was of long duration, while in 20 per cent it started within six months of the onset of malignant hypertension. In the remaining patients, nocturia occurred during the illness. The frequency of urination ranged from one to six times a night, both in patients in whom the symptom was of long duration and in those in whom it was of recent origin. In patients known to have glomerulonephritis, the frequency of urination averaged four to five times a night; in those with pyelonephritis or nephrosclerosis, it averaged two to three times a night. On the whole, nocturia was of little help in differential diagnosis and was in no way characteristic of malignant hypertension.

Symptoms of acute renal infection were relatively infrequent; when they occurred it was long before the onset of malignant hypertension. Dysuria and frequency were each mentioned by fifteen patients, and pain or tenderness in the costovertebral area by twenty-one. Nine patients, six of whom had pyelonephritis, had a combination of these symptoms. It is interesting that almost as many patients with glomerulonephritis (three) complained of pain in the renal area as did those with pyelonephritis (four).

Cultures were made of the urine of twenty-seven patients. The cultures revealed organisms in eleven instances; in these patients, pyelonephritis was the only lesion found at operation or post-mortem examination.

Proteinuria was a common manifestation of renal damage; it occurred at some time during the illness in all but three of our patients. In other studies of malignant hypertension, as many as 10 per cent of the patients were reported to have no albuminuria early in the course of the disease. In ten patients (10 per cent) of our group, the urine was free of albumin at the time of discovery of Keith-Wagener IV retinitis or shortly thereafter. In two other patients, the urine was free of albumin during the month preceding discovery of papilledema.

In the remaining ninety-four patients in the group, some albumin was present in the urine when papilledema was present. Did the estimated amounts have any significance? If so, it

appeared to be that those who excreted 3 to 4 plus albumin in the urine were seen later in the course of the disease. There were forty-eight such patients, twenty-four of whom came to autopsy. Of the latter, nine had nephrosclerosis, eleven pyelonephritis, and four glomerulonephritis. The presence of large amounts of albumin in the urine, therefore, is of little aid in differential diagnosis. Of twenty-three patients who showed no more than a trace of albumin in the urine, only two came to autopsy, both at another hospital. According to the death certificates, the two patients had hypertensive cardiovascular disease. In one patient in this group, a renal biopsy taken during sympathectomy showed early nephrosclerosis.

More accurate determinations of the loss of protein were given by Addis and Esbach tests. The results of these tests during or after the discovery of papilledema showed the distribution noted in Table VI. When serial tests showed a shift from one group to another (as it did in eight cases), the patient was included in both. Tests reported in grams per liter were converted to grams per twenty-four hours.

Protein (grams) per twenty-four hours, in the presence of papilledema in forty-eight patients, is shown in Table VI.

TABLE VI. PROTEIN EXCRETION IN 48 PATIENTS WITH PAPILLEDEMA

.000-0.05	4 Patients			
.051-1.9	16 Patients	3 Nephrosclerosis	1 Pyelonephritis	
2.000-3.9	17 Patients	3 Nephrosclerosis	5 Pyelonephritis	3 Glomerulonephritis
4.000 and over	19 Patients	4 Nephrosclerosis	7 Pyelonephritis	1 Glomerulonephritis

Thus, one-third of the group was excreting over 4 Gm. of albumin per twenty-four hours, and an almost equal number was losing between 2 and 4 Gm. per twenty-four hours. The autopsy correlation shows that urinary excretion of large amounts of protein is not helpful in differential diagnosis, but that nephrosclerosis is probably the likely lesion in the presence of minimal proteinuria.

Routine examination of urinary sediment was also made at the time papilledema was discovered. In approximately three-fourths of the patients, the sediment did not show an abnormal number of white blood cells. When an excessive number of white blood cells appeared, chronic pyelonephritis was by far the most frequent lesion found at autopsy, although both nephrosclerosis and glomerulonephritis also occurred. An increase in the number of red blood cells was twice as frequent in glomerulonephritis as in other lesions.

Addis counts were performed in forty-two patients. The results were normal in respect to cellular elements in only about one-fourth of the instances. The discrepancy in results of the two examinations (routine analysis and Addis count) can be explained by the greater accuracy of the Addis count and also by the fact that only patients who showed abnormal urine sediments on routine tests were selected for Addis tests. Again, when large numbers of white blood cells were present in the urine, pyelonephritis was the most frequent diagnosis at autopsy. It is interesting, however, that in one patient with chronic pyelonephritis, the number of white blood cells was normal.

Blood chemistry determinations were made on all patients during the course of the disease, particularly during the terminal stage. On the whole, they were not useful in establishing the type of basic renal lesion, but they were helpful in following the progression of renal damage and in determining which patients had passed the stage of definitive treatment.

Roentgenographic examination of the kidneys in sixty-one patients revealed abnormalities in thirty-five. Poor excretion of dye on intravenous pyelography, the most frequent abnormality, was manifested by ten patients, in three of whom the nonprotein nitrogen level and phenolsulfonphthalein excretion were normal at the time. Two patients were uremic and the remaining fifty-nine showed moderate impairment of renal function at the time of examination. Renal calculi were suspected in five patients; their presence was confirmed in one at autopsy (No. 54). Atrophy of one kidney was demonstrated by intravenous pyelograms and retrograde studies in Patients 73, 81, and 99. The weight of the kidney of Patients 73 and 81 was 106 grams and 50 grams,

respectively. In Patient 99, both kidneys were still functioning. Bilateral atrophy was demonstrated in Patients 60 and 80. Patient 80 had chronic pyelonephritis; the kidneys weighed 45 and 50 grams. In Patient 42, no right kidney was demonstrated by either intravenous pyelograms or retrograde studies, and the left was described as enlarged. At autopsy he was found to have had chronic pyelonephritis; the right kidney weighed 8 grams and the left 240 grams. Enlarged kidneys were also described in Patients 62 and 88; the weight of the kidneys at autopsy was not available. Congenital anomalies included a bifid left renal pelvis in Patient 24, bilateral double renal pelvis in Patient 104, and malrotation with horseshoe kidney in Patient 107. These anomalies were confirmed at autopsy in the last two patients. Hydronephrosis was described in Patient 103, a 26-year-old man, who had suffered since birth from incontinence and repeated attacks of pyelonephritis. A retroperitoneal mass was suspected in Patient 8, but was not found at operation or post-mortem examination. In general, the changes demonstrable by roentgenographic examination were verified at autopsy. Since structural abnormalities were found in 40 per cent of the patients examined, such studies seem justified in patients with malignant hypertension.

The differential diagnosis of the basic renal lesions in malignant hypertension was considered of primary importance, since the treatment appeared to be more successful in patients with primary nephrosclerosis. Table VII correlates autopsy data with simple renal function tests.

TABLE VII. RENAL FUNCTION STUDIES CORRELATED WITH AUTOPSY FINDINGS

	NUMBER OF PATIENTS	DIAGNOSIS AT AUTOPSY
<i>Routine urinalysis or concentration test after development of K-W IV* retinitis (highest specific gravity)</i>		
1.020 or above	35	8 nephrosclerosis
1.014 or below	47	6 nephrosclerosis 4 glomerulonephritis 10 pyelonephritis
<i>First phenolsulfonthalein test after discovery of K-W IV* retinitis</i>		
Normal (over 50% in 2 hours or 25% in 15 minutes)	24	7 nephrosclerosis 1 glomerulonephritis
Impaired (21-49% in 2 hours or 11-24% in 15 minutes)	30	4 nephrosclerosis 1 glomerulonephritis 2 pyelonephritis
Failing (under 20% in 2 hours or under 10% in 15 minutes)	24	2 nephrosclerosis 3 glomerulonephritis 7 pyelonephritis

*Keith-Wagener Group IV.

In patients with Keith-Wagener IV retinitis, a normal finding in two common tests of renal function (concentrating ability and phenolsulfonthalein excretion) occurred almost exclusively in patients with primary nephrosclerosis, as proved by autopsy diagnosis. The one exception was a patient with glomerulonephritis who showed a normal excretion of phenolsulfonthalein, although he had papilledema.

TABLE VIII. COURSE OF MALIGNANT HYPERTENSION IN 37 PATIENTS

PATIENT	SEX	AGE	DURATION OF HYPERTENSION	INITIAL SYMPTOM	INITIAL RENAL STATUS	PROGRESSION OF LESION
5	M	61	8 mo.	Blurred vision	Dehydration; sp.gr. 1.020; tr. alb.; PSP 38% 2 hr.; NPN 52	Died 2 mo. of uremia, terminal NPN 201.
7	F	38	7 mo.	Blurred vision	sp.gr. 1.022; 3+ alb.; PSP 35% 2 hr.; NPN 25-35	Observed 2 mo. without develop. impairment
8 (Neph.)	M	47	2 yr.	Gross hematuria	sp.gr. 1.012; tr. alb.; PSP 67% 2 hr.; NPN 35	4 mo. later PSP 30% 2 hr., NPN 48; Urine 4+ alb.
9 (Neph.)	F	39	3 yr.	Visual loss	sp.gr. 1.007; 3+ alb.; PSP 53% 2 hr.; NPN 27	2 mo. later PSP less than 5% 2 hr.; NPN 83
10	F	37	2 yr. a dx	Epig. pain, n. & v.	Dehydration; sp. gr. 1.028; 2+ alb.; PSP 34% 2 hr.; NPN 23	
12	M	37	7 mo.	Cardiac asthma	sp.gr. 1.027; tr. alb.; PSP 33% 2 hr.; NPN 48	Developed uremia 4 mo. later
15	M	32	9 mo.	Visual loss	Dehydration; sp.gr. 1.017; 0.9 Gm. alb./24 hr.; PSP 50% 2 hr.; NPN 24-43	
18	M	45	6 mo.	Severe h.a.'s	sp.gr. 1.024; 3+ alb.; PSP 54% 2 hr.; NPN 55-41	Died 3 mo. later in uremia
22 (Neph.)	F	35	2 yr.	Hematuria	Dehydration; sp.gr. 1.021; 3 Gm. alb./24 hr.; PSP 55% 2 hr.; NPN 38	One week later PSP 35% 2 hr., & 1 mo. later NPN 91; d. in uremia 5 wk. p normal PSP
26 (Gl. neph.)	M	21	2 1/4 yr.	Blurred vision	Dehydration; sp.gr. 1.019; 3 Gm. alb./24 hr.; PSP 65% 2 hr.; NPN 29	1 mo. later PSP 45% 2 hr.; 14 mo. later, NPN 177, d.
33	F	43	17 yr.	Acute h.a., n. & v.	sp.gr. 1.025; 1+ alb.; PSP 42% 2 hr.; NPN 48-32	Died 6 mo. later in uremia
38	M	61	11 yr.	Blurred vision	Dehydration; sp.gr. 1.021; no alb. initially; PSP 50% 2 hr.; NPN 39	
40	M	59	5 yr.	Visual loss	sp.gr. 1.017; ft. alb.; PSP 83% 2 hr. and 65% 4 mo. later	
43	F	49	12 yr.	Scotomata	Dehydration; sp.gr. 1.016; no alb. 1 mo. p dx, PSP 53% 2 hr. 4 yr. later, sp.gr. 1.020 5 yr.	
50	M	52	4 yr.		Dehydration; sp.gr. 1.028; tr. alb.; PSP 45% 2 hr.; NPN 31 15 mo. p dx	

SEEN INITIALLY WITH SATISFACTORY RENAL FUNCTION

	CARDIAC COURSE	CEREBRAL COURSE	RETINAL COURSE	X-RAY FINDINGS AND TREATMENT	SURVIVAL AFTER FIRST K-W IV (MO.)
terminal	Sympts failure 1 yr. ACD enlarged, ECG no characteristic pattern	Dizziness 1 yr.; 1 episode unconsciousness	K-W IV	I.V.P., poor dye excretion	2
develop.	Sympts failure 1 yr., ACD enlarged, arrhythmias		K-W IV	Retrogrades within normal limits	2
hr., alb.	Terminal failure only, ACD enlarged but x-ray wnl at diagnosis	H.a.'s 1 yr., unequal pupils; + Romberg	K-W IV—no hemorrhages or exudates for 4 mo.	Unilateral adrenalectomy (died p-o) Retro: ?retroperitoneal mass?	4
n 5%	Terminal failure only, ACD enlarged, ECG and x-ray wnl	Severe h.a. 3 yr., convulsions 1½ yr.	K-W IV	I.V.P. wnl	3
	Sympts failure 2 mo. a KW IV, ACD enlarged, pulm. edema in hosp. ECG characteristic LVH, x-ray showed LVH		K-W IV, no symptoms		
later	Failure at time of onset, ACD enlarged, ECG showed LVH, x-ray wnl.		K-W IV, no symptoms	I.V.P. wnl	6
	Failure (pnd) 4 mo. a KW IV, ACD enl., decomp. X-ray 40% enlarged, ECG showed probable LVH		K-W II to K-W IV in 3 weeks	I.V.P. wnl	3
ia	No sympts, ACD enlarged, x-ray 15% enlarged, ECG consistent with LVH		K-W IV	I.V.P. wnl	3
2 hr., 01; d. in al PSP	Sl. enlarged, no failure, ECG showed "early LVH," x-ray showed slight enlargement		K-W III to IV in 14 mo.	I.V.P. wnl	1
ar.; 7, d.	ACD wnl, ECG hi volt, x-ray 15% enl. at diag., volt. wnl po, sympts fail. 12 mo. p dx, signs & enl ACD 14 mo. p dx.	Terminal convulsions	K-W IV to K-W II p-o; to IV 7 mo. later; no hemm. or ex. term., but with pap.	I.V.P. wnl, sympathectomy	14
ia	Failure devel. 1 wk. a dx, ACD enl, decomp., x-ray showed marked enlargement	Psychosis on wards	K-W IV		6
	No signs of failure, ACD not enl. but LVH by x-ray and ECG.	Subarachnoid hemms., died of CVA	K-W IV		15
	Sympts failure 1 yr, ACD enl & decomp at onset, ECG & x-ray char. LVH		K-W IV	I.V.P. wnl	5
	LVH by PE, ECG, x-ray from dx on; no failure but angina. Died of ruptured aorta	Mild CVA with residual 2 yr. before death	K-W I to IV in 5 yrs.; regressed to II in 32 mo., to IV 3 yr. later	I.V.P. wnl	78
	S.O.B. 3 yr., angina 5 a dx; no signs; ECG showed LVH		K-W III to IV in 6 mo.; 11 mo. later K-W III, spont. regression		29

TABLE VIII. COURSE OF MALIGNANT HYPERTENSION IN 37 PATIENTS

PATIENT	SEX	AGE	DURATION OF HYPERTENSION	INITIAL SYMPTOM	INITIAL RENAL STATUS	PROGRESSION OF LESION
59 (Neph.)	F	50	7 yr.		sp.gr. 1.022; tr. alb.; PSP 59% 2 hr.	
62 (Neph.)	F	35	12 mo. a dx	Blurred vision	Dehydration; sp.gr. 1.015; tr. alb.; PSP 52% 2 hr.; NPN 28	22 mo. later: dehyd, sp.gr. 1.022-1.030, PSP 44% 2 hr.
63	M	25	9 yr.	Blurred vision	sp.gr. 1.015; tr. alb.; PSP 65% 2 hr.; NPN 32	8 mo. later PSP 39% 2 hr., NPN 32, episodes of hema- turia
65	M	52	7 yr.	Blurred vision	sp.gr. 1.026; tr. alb.; PSP 63% 2 hr.; NPN 35	
66	M	55	3 yr.	Blurred vision	sp.gr. 1.018; tr. alb.; PSP 57% 2 hr.	4 mo. later hematuria, NPN 26
67	M	59	5 mo.	Severe h.a., blurred vision	sp.gr. 1.023; 2+ alb.; PSP 53% 2 hr.; NPN 34	Died in uremia 3 mo. later; hematuria
69	F	37		Blurred vision	Dehydration; sp.gr. 1.023; 2.7 Gm. alb./24 hr.; PSP 65% 2 hr.; NPN 38	
73	M	39	11 yr.	Blurred vision	sp.gr. 1.025; no alb.; PSP 44% 2 hr., p-o 57% 2 hr.	Normal function, no alb., 11 yrs. later
74	F	35	13 yr.	Severe h.a.'s	sp.gr. 1.016; 2+ alb.; PSP 75% 2 hr.; NPN 33	
75	M	66	18 mo.		Dehydration; sp.gr. 1.022; tr. alb.; PSP 35% 2 hr.; NPN 32	
79	F	40	18 yr.	Blurred vision	sp.gr. 1.010; no alb.; PSP 30% 15 min.	
85	F	42	50 mo.	Blurred vision	sp.gr. 1.020; 2+ alb., later none; PSP 27% 2 hr.; NPN 30	2 yrs. later PSP 42% 2 hr., dehyd., sp.gr. 1.003
87	F	32	14 yr.	Blurred vision	Dehydration; sp.gr. 1.025; no alb.; PSP 100% 2 hr.; NPN 23	8 mo. later dehyd, sp.gr. 1.023, PSP 50% 30 min.
88	M	42	7 yr.	Gross hematuria	Dehydration; sp.gr. 1.026; .14 Gm. alb./24 hr.; PSP 45% 15 min.	Devel. hematuria 5 mo. later, PSP 70% 2 hr., NPN 31
89	M	19	6 yr.		sp.gr. 1.020; no alb.; PSP 44% 15 min. (4 mo. p dx)	22 mo. later, PSP 65% 2 hr., 3+ alb.

SEEN INITIALLY WITH SATISFACTORY RENAL FUNCTION (CONTINUED)

CARDIAC COURSE	CEREBRAL COURSE	RETINAL COURSE	X-RAY FINDINGS AND TREATMENT	SURVIVAL AFTER FIRST K-W IV (MO.)
Symptoms failure 3 mo. a dx; ACD enl; ECG prob. LVH; died of coronary		K-W IV, unilateral papilledema; regressed		86
ACD & x-ray sl. enl. at time of dx; ECG LVH; changed toward normal po; decomp. 16 mo. p dx.	Unconscious 2 days c convulsions 1 mo. a dx.	K-W I to IV in 7 mo.; 21 mo. later still pap., but no hemm. or exud.	Sympathectomy; I.V.P. showed slightly enlarged left kidney	
ACD enl., ECG no char. pattern; x-ray LVH, develop. dyspnea 8 mo. p dx.	Episodes of facial palsy, Dd "encephalomalacia"	K-W IV	I.V.P. showed poor dye excretion	11
No sympts, ACD enl, LVH by fluoroscopy	2 CVA's, 3 yr. a and at time of death	K-W IV		82
No symptoms, ACD enlarged	Tr. aphasia	K-W IV	I.V.P. wnl	13
ACD enl. at time of dx, ECG no char. pattern, x-ray contour LVH	Onset with severe h.a. p blast; trauma-episodes of confusion	K-W IV		3
Sympts failure 1 yr a KW IV; no enl. or decomp by PE, ECG & x-ray LVH		K-W IV	I.V.P. wnl	
Normal PE & ECG		K-W IV regressed immed. p-o; 11 yrs. later K-W II	Nephrectomy; I.V.P. showed small non-functioning right kidney, left wnl.	132 (living)
Orthopnea only ACD enl., ECG & x-ray LVH	Dd CVA	K-W II to IV in 5 yr.	Retrogrades wnl	9
No sympts, PE wnl except for many pmb's	Ataxia, + Romberg	K-W IV		7
PE wnl, also ECG, x-ray		K-W IV to III after 7 mo.	Low sodium diet, I.V.P. wnl	32 (living)
Mild s.o.b., no decomp., ACD sl. enl'd, LVH present by ECG, x-ray		K-W IV to II in 9 mo.	Low sodium diet, I.V.P. wnl	48 (living)
No failure, ACD sl. enl. but ECG wnl.		Unilat. pap. regressed by 9 mo. p dx. & operation	Sympathectomy, I.V.P. wnl	32 (living)
No sympts, ACD sl. enl., x-ray wnl, ECG showed coronary artery disease	Died CVA	Unilat. pap. progr. to bilat. in 5 mo.; regressed to K-W II in 2 mo. p-o.	Sympathectomy, I.V.P. left renal calculus with min. enl. of kidney	15
wnl at dx, onset sympts failure 2 mo. p dx; 22 mo. p dx ACD enl, x-ray wnl; ECG prob LVH; died in failure	Brief diplopia	K-W IV, asymptomatic for 7 mo., regr. 2 mo. p-o, 1 mo. before death	Sympathectomy, I.V.P. wnl	27

TABLE VIII. COURSE OF MALIGNANT HYPERTENSION IN 37 PATIENTS

PATIENT	SEX	AGE	DURATION OF HYPERTENSION	INITIAL SYMPTOM	INITIAL RENAL STATUS	PROGRESSION OF LESION
90	M	49	5 yr.	Visual loss	sp.gr. 1.018; 3+ alb.; PSP 50% 2 hr.; NPN 38	
91	M	45	2 yr.	Visual loss	Dehydration; sp.gr. 1.020; .7 Gm. alb./24 hr.; PSP 38% 2 hr.; NPN 41	3 mo. later NPN 60
92	F	53	10 yr.	Blurred vision	sp.gr. 1.026; 3+ alb.; PSP 11% 2 hr.; NPN 48	NPN 71 6 wk. later
96	M	33	9 yr.		sp.gr. 1.016; no alb. at dx; p 6 mo. 1.020 sp.gr.; NPN 31	PSP 56% 2 hr. 30 mo. before
99	F	30	2 yr.	h.a., visual loss	Dehydration; sp.gr. 1.021; 3+ alb.; PSP 71% 2 hr. (2 mo. p dx); NPN 31	
101	M	23	3 yr.	Visual loss	Dehydration; sp.gr. 1.023; 3 Gm. alb./24 hr.	
104	F	13	2 mo.	Blurred vision	sp.gr. 1.028; 2+ alb.; PSP 45% 15 min.	

MALIGNANT HYPERTENSION IN THE PRESENCE OF NORMAL RENAL FUNCTION

In the total series there were thirty-seven patients who, when seen initially, had satisfactory renal function in the presence of papilledema (see Table VIII). Renal function was considered satisfactory, although not necessarily normal, if the urine had a specific gravity of 1.020 or above with less than 4 plus albumin, or if the phenolsulfonthalein excretion was over 50 per cent in two hours. The progression of the disease in this group was of particular interest, since the presence of adequate renal function is necessary for modern forms of therapy. Table IX summarizes the course of the disease in each of the thirty-seven patients. In this group the average survival of the untreated members was 16.3 months; the average survival of treated and untreated patients was 22.4 months, as compared with 8.4 months in the entire group. Table X summarizes the course of the disease in the total series of 104 cases.

In twenty-four of the thirty-seven patients, the onset was marked by visual loss, in three by hematuria, and in three by headache. Cardiac asthma and an acute gastrointestinal upset marked the onset in two patients. In five patients, there were no definite initial symptoms.

SEEN INITIALLY WITH SATISFACTORY RENAL FUNCTION (CONTINUED)

CARDIAC COURSE	CEREBRAL COURSE	RETINAL COURSE	X-RAY FINDINGS AND TREATMENT	SURVIVAL AFTER FIRST K-W IV (MO.)
ACD enl, x-ray & ECG showed LVH; mild s.o.b. only	Died of CVA	K-W IV	I.V.P. poor excretion but wnl	3
ACD enl, ECG & x-ray showed LVH; sympts failure devel. at time of onset; signs 3 mo. later		K-W IV	Low sodium diet	5
Sympts failure 8 mo a dx, severe at onset, ACD enl, decomp, x-ray & ECG showed LVH	CVA just a dx; transient changes	K-W IV		2
No sympts; sl. enl. at dx; x-ray 10%; ECG "suggests LVH"; angina 14 mo. after diagnosis		K-W I to III in 6 mo., III to IV in 15 mo., regressed 6 mo. p-o	Sympathectomy, I.V.P. wnl	46 (living)
No sympts, PE, ECG, x-ray wnl.		K-W IV to II in 12 mo.	Low sodium; retrogrades wnl	21 (living)
No sympts; ECG showed high voltage only; x-ray wnl.	Convulsions 6-8 mo. a dx, recurrent thereafter	K-W III to IV in 1 mo., regressed to II 1 mo. p-o	Low medium and sympathectomy, I.V.P. wnl	15
No sympts or enl. at dx; developed murmur after 3 wks.; ECG showed low T ₂ ; x-ray wnl.		K-W IV	First stage sympathectomy, died p-o, I.V.P. double renal pelvis	1

Hypertension was known to exist in all thirty-seven patients before papilledema was discovered, although in several instances, it was recognized less than one month before. In two patients, it had been found more than fifteen years before papilledema was noted.

The development of renal impairment in this group was of special significance, since recent work has shown that such forms of therapy as sympathectomy and pyrogen treatment are of no avail when renal function is seriously impaired. Renal failure was striking in the rapidity of its development, as well as by its occasional absence. The observations were too few and too random to permit calculation of an average "period of grace" before development of renal impairment.

Impairment occurred in as short a time as one week and uremia developed in one month in one patient (No. 22). This patient, a 34-year-old housewife, was first seen in the Hypertension Clinic in September, 1945. She had known of elevated blood pressure for one year, and at that time heart and kidney function were normal, although a Keith-Wagener III retinitis was present. She complained of headaches and fatigue, which in October, 1946, grew worse and were accompanied by nausea and vomiting. In November, 1946, the retinae showed 1- to 2-diopter elevation of the discs, moderately severe vascular changes, hemorrhage and exudate. Phenolsulfonthalein excretion on Nov. 6 was 55 per cent in two hours (volume 125 c.c.); one week later it was 35 per

TABLE IX. COURSE OF MALIGNANT HYPERTENSION IN 37 PATIENTS WHOSE RENAL FUNCTION WAS SATISFACTORY AT ONSET

	TOTAL	PAPILLEDEMA REVERSED	SURVIVAL OVER 18 MONTHS	SURVIVAL OVER 30 MONTHS
No "specific" treatment	24	3*	4	3*
Sympathectomy	7	6†	4	3
Low sodium, rice diets	5	3	3	2
Nephrectomy	1	1	1	1

*2 had unilateral papilledema.

†1 had unilateral papilledema.

cent in two hours (450 c.c.) and she was having hematuria. On Nov. 21 the nonprotein nitrogen was 38 mg. per cent but by Dec. 4, just one month after a test showed a normal phenolsulfonthalein excretion, the nonprotein nitrogen had risen to 91 mg. per cent. She died of uremia on Dec. 16, 1946, and at autopsy was found to have malignant nephrosclerosis. Three other patients developed uremia within two months after normal function studies were done; and nine became uremic in six months or less. Satisfactory renal function may continue much longer in some untreated patients with papilledema, but since this is unpredictable and unusual in our experience, it is unwise to delay vigorous therapy.

Roentgenographic Findings.—Pyelograms in twenty-seven of this group of thirty-seven patients showed that the majority had normal kidneys. No evidence of disease was found in twenty-two patients, although in four excretion of dye was poor. Of the remaining five patients, No. 88 had a renal calculus with minimal enlargement of the kidney; No. 104 had double renal pelvises; No. 62 was considered to have a minimally enlarged left kidney; No. 73 had a small nonfunctioning right kidney, and since nephrectomy eleven years previously has been asymptomatic; No. 8 was thought to have a retroperitoneal mass, which, however, was not found at operation or post-mortem examination. The incidence of abnormalities in this group with satisfactory renal function was 18 per cent, as opposed to 40 per cent in the entire group.

The cardiac manifestations of the disease in the thirty-seven patients with satisfactory renal function at the time of diagnosis were not remarkably different from those in the group as a whole. Almost one-half developed signs and symptoms of congestive failure; one-fifth were in failure before the discovery of papilledema. These percentages are virtually the same as those for the total group. Physical examination at the time of diagnosis revealed cardiac enlargement in 75 per cent in both groups. Electrocardiographic interpretations were: left ventricular hypertrophy in 66 per cent of the patients with satisfactory renal function and 70 per cent of the total group. Roentgenogram films showed enlargement of the heart in 69 per cent in the former, as opposed to 75 per cent in the whole series. Although renal function was significantly better in these thirty-seven patients than in the group as a whole, the cardiac status of both groups was essentially the same.

TABLE X. COURSE OF MALIGNANT HYPERTENSION IN TOTAL SERIES OF 104 CASES INCLUDING 37 CASES MENTIONED IN TABLE IX

	TOTAL	PAPILLEDEMA REVERSED	SURVIVAL OVER 18 MONTHS	SURVIVAL OVER 30 MONTHS
No "specific" treatment	88	3*	4	3*
Sympathectomy	7	6†	4	3
Low sodium, rice diets	8	5	3	2
Nephrectomy	1	1	1	1

*2 had unilateral papilledema.

†1 had unilateral papilledema.

The effect of the disease on the central nervous system was essentially the same in both groups. There was no more than a 5 per cent difference in the frequency with which cerebrovascular accidents and convulsions occurred in the two groups.

The importance of satisfactory renal function in the possible regression of papilledema is emphasized by the fact that the only three patients in our series whose papilledema subsided without specific treatment had satisfactory renal function when first seen. Twelve other patients whose papilledema regressed with specific treatment (sympathectomy, low sodium diet, nephrectomy) had satisfactory renal function when treatment was initiated.

SUMMARY.—The importance of the kidney in malignant hypertension is impressive. In our series, 84 per cent of patients had symptoms due to the effect of the disease on the kidney. The most striking symptom was gross hematuria, which occurred at some time during the course of the illness in 26 per cent of the patients. In the majority of these patients, glomerulonephritis or nephrosclerosis was the basic renal lesion. Proteinuria was manifested by all but ten patients at the time of diagnosis; it developed subsequently in seven of the ten. Its absence appeared to be a favorable prognostic sign. In two-thirds of the patients, over 2 Gm. of albumin were excreted in twenty-four hours.

Blood chemistry studies were felt to be of aid in following the progress of renal damage and in directing electrolyte replacement therapy. Roentgenographic examination of the kidneys, made on 60 per cent of the patients, showed structural abnormalities in 40 per cent of the group examined. These corresponded remarkably well with the autopsy findings. The impression that nephrosclerosis is the most likely lesion when good renal function is retained in the presence of hypertension and Keith-Wagener IV retinitis was also verified by autopsy correlation. This is the only time when differential diagnosis of the basic renal lesion is of more than academic importance, since therapy can be only palliative in the presence of renal failure. In thirty-seven patients, papilledema was discovered while adequate renal function remained. This group was felt to represent almost exclusively cases of primary nephrosclerosis. The survival of these patients was significantly increased, averaging 16.3 months in the untreated cases. Impairment of renal function was observed to develop in as short a period as one week and actual uremia frequently occurred in less than six months from the time of diagnosis. Structural abnormalities were demonstrated by roentgenographic examination in 18 per cent. The cardiac and cerebral manifestations of the disease were not significantly different in the patients with good renal function initially, but the retinal changes showed more than ten times the incidence of reversal of papilledema. The rapidity with which renal impairment may develop in this disease must again be stressed, in the hope of urging early diagnosis and prompt therapy. It is this group of patients with satisfactory renal function in whom early and vigorous therapy may halt the course of malignant hypertension.

THE HEMATOPOIETIC SYSTEM IN MALIGNANT HYPERTENSION

Sixty patients in our series showed a tendency to bleed, although in some instances the bleeding may have been due to causes other than malignant hyper-

tension. Bleeding from the kidneys occurred in thirty patients, the nose in nineteen, gastrointestinal tract in fifteen, skin in thirteen, lungs in six, and joints in one. Forty per cent of the patients with a tendency to bleed were uremic. There appeared to be no correlation between the basic renal lesion and the absence or presence of bleeding or its site. In general, bleeding occurred late in the course of the illness.

Table XI gives the distribution of hemoglobin values found at the time of appearance of Keith-Wagener IV retinitis. Determinations were made on all but seven patients.

TABLE XI. HEMOGLOBIN VALUES FOUND AT TIME OF APPEARANCE OF KEITH-WAGNER IV RETINITIS

HEMOGLOBIN LEVEL	NUMBER OF PATIENTS	POST-MORTEM OR OPERATIVE DIAGNOSIS
12.5 Gm. (86 %) or above	49	10 nephrosclerosis 1 glomerulonephritis 3 pyelonephritis
9.0 Gm. (62%)–12.4 Gm.	38	2 nephrosclerosis 3 glomerulonephritis 1 pyelonephritis
8.9 Gm. or less	10	3 nephrosclerosis 3 glomerulonephritis 1 pyelonephritis

In five patients, the hemoglobin level fell below 8.9 Gm. while they were under observation. Four of these patients had pyelonephritis, and one had nephrosclerosis. All but three of the fifteen patients with severe anemia were uremic at the time, and in two of the others, the nonprotein nitrogen was between 50 and 60 mg. per cent. None of these patients had profound loss of blood, except the nonuremic patient (No. 63), who was apparently losing large quantities in tarry stools.

The hematopoietic system was affected in at least one-half of our patients with malignant hypertension. A little over one-half of our group showed a tendency to bleed. Uremia was twice as common in these patients as in the patients with no tendency to bleed. A moderate or severe anemia was present in half the group at the time when papilledema was discovered. In the fifteen patients who developed severe anemia, uremia appeared to be the predominant cause. Nephrosclerosis is the most likely lesion when the hemoglobin level is normal at the time of diagnosis of malignant hypertension.

AUTOPSY RESULTS

Autopsy was performed on thirty-five patients. In two cases, diagnoses were made from surgical or biopsy specimens, and in 5 cases from coroner's examinations.

A major renal lesion was found in thirty-one of these thirty-five patients; twelve had nephrosclerosis, twelve had pyelonephritis, and seven had glomerulonephritis. In only one of the patients with glomerulonephritis (No. 26) was arteriolar necrosis superimposed upon another renal lesion.

The course was different from that of others with the same lesion, in that good renal function and hemoglobin level were maintained at the time when papilledema appeared. In the patients with chronic pyelonephritis, no arteriolonecrosis occurred; the vascular changes were limited to hypertrophy, sclerosis and occlusion. Three of the patients with nephrosclerosis were described as showing arteriolonecrosis (Patients 4, 22, and 100).

The autopsy which produced the greatest surprise was performed on a 13-year-old school girl.

Patient 104 had suffered loss of vision in April, 1946, which led to the discovery of hypertension. Other complaints included palpitation and noctuidosis. When the patient was seen in June, 1946, the blood pressure was 130-205/95-158 and the retinae were classified as Keith-Wagener IV. The heart and kidneys appeared normal. A sympathectomy was performed on July 31, 1946. The patient went into circulatory and respiratory collapse postoperatively and died the same day. Examination at autopsy revealed retroperitoneal and bilateral adrenal chromaffin tumors.

In one other patient, the hypertension was secondary to an endocrine disorder. This woman (No. 29) had clinical signs typical of Cushing's disease for five years preceding the onset of the malignant phase of hypertension. The adrenals weighed 11.9 and 15.7 grams.

In conclusion, autopsies were performed on thirty-five of our patients. The results indicated that approximately 89 per cent of this group of patients with the clinical syndrome of malignant hypertension had a major renal lesion. Of these, approximately 40 per cent had pyelonephritis (six men and six women) and 20 per cent had glomerulonephritis. The remaining 40 per cent showed only changes due to malignant nephrosclerosis. Actual arteriolonecrosis was relatively rare; it occurred in only four patients, three of whom had nephrosclerosis.

INFLUENCE OF TREATMENT ON THE COURSE OF THE DISEASE

Before the use of sympathectomy, low sodium diet, and the newer sympatholytic drugs, treatment of malignant hypertension was symptomatic or concerned with vascular complications, such as cardiac failure, renal failure, cerebrovascular accidents, and similar conditions. With this program of nonspecific care, the course of the disease was almost universally downhill; only three of our eighty-eight patients who received such treatment survived thirty months, and 50 per cent died within three months. That this downhill course can be reversed in some patients by treatment is apparent from Table X, which summarizes our experiences with treatment with respect to reversal of papilledema and survival longer than thirty months. This data is for treatment prior to 1951, when hexamethonium therapy was begun in our clinic. As of June, 1952, we have seen reversal of papilledema in eight of thirteen patients with malignant hypertension who were treated with hexamethonium administered subcutaneously, but it is too soon to comment on length of survival. Treatment is not the primary consideration of this paper, but Table X is included to emphasize that with modern therapy the prognosis in malignant hypertension is not hopeless. Apparently, reversal of papilledema is essential to survival, although some of our patients who improved initially with loss of papilledema died within two years, despite specific treatment, because of cerebral or cardiac failure. No patient whose renal function was seriously impaired when the patient was first seen survived thirty months.

DISCUSSION

This study confirms the unfavorable prognosis described by Keith and Wagener¹⁴ for patients with hypertension and papilledema who receive sympto-

matic and nonspecific treatment. The appearance of papilledema in a hypertensive patient indicates occurrence of a phase of the disease which, if left untreated, usually results in a rapidly downhill course. There are rare exceptions to this statement, but Keith and Wagener¹⁵ were able to find only fifteen such instances in twenty years. In our own series, recession of papilledema occurred spontaneously in only three patients. Keith and Wagener¹⁵ have discussed the mechanism of this neuroretinopathy; they do not believe that increased cerebrospinal fluid pressure is responsible for the papilledema, but concluded that the most probable mechanism is "decompensation of the circulation in the optic nerve, retina and choroid." Our demonstration of normal spinal fluid pressures in eighteen patients (38 per cent) also makes it appear doubtful that increased cerebrospinal fluid pressure alone was responsible for the papilledema. In addition, unilateral papilledema would be difficult to explain on the basis of a generalized increased spinal fluid pressure. Regardless of its mechanism, the ominous prognostic significance of papilledema must be appreciated. Not all patients with rapidly progressive hypertension exhibit this neuroretinopathy. Goldring and Chasis⁸ estimated that approximately 20 per cent of patients in whom the disease runs such an adverse course do not have papilledema.

The importance of the function of the kidney in the prognosis of hypertensive patients with papilledema also is emphasized in our cases. Renal function was satisfactory in each of the three patients in whom spontaneous reversal of papilledema occurred. Furthermore, satisfactory renal function was necessary for the successful use of sympathectomy or a low sodium diet in treatment. If renal function is impaired, use of the newer drugs, such as Dibenamine,¹² hexamethonium,³³ or the veratrum or dihydroergotamine alkaloids,^{2,6,33,48} is the treatment of choice. The rapid deterioration of renal function which may occur in patients with malignant hypertension was impressive and underlined the need for frequent observations of renal function and early institution of a therapeutic program.

The high incidence of chronic pyelonephritis (40 per cent) in the small number of our patients examined at autopsy is of interest. The fact that the pathologic findings came as a surprise in some instances emphasizes the need for considering pyelonephritis in all patients with malignant hypertension. The ten-year survival and probable "cure" in one man who underwent a nephrectomy for atrophic pyelonephritis, and the reversal of papilledema following nephrectomy in a seriously ill woman (seen after the present series was completed) indicate the importance of unilateral atrophic pyelonephritis. Such a lesion is rare, but the results of nephrectomy were gratifying in these two patients.

SUMMARY

Material for this study consisted of the 104 cases of malignant hypertension seen at the University of California Hospital from 1936 through 1949. Follow-up information was obtained on all patients. The general features which distinguished the group were the following:

1. The average age was 42 years.
2. The ratio of men to women was 3:2.
3. A family history of hypertension was found in half the patients.

4. Knowledge of pre-existing hypertension was present in 71 per cent of the group.
5. Significant past illnesses (scarlet fever or frequent sore throats, glomerulonephritis, pyelonephritis, and toxemia of pregnancy) had occurred in 56 per cent of the patients.

An effort was made to determine the actual duration of the syndrome of malignant hypertension by estimating the date of onset from the patient's history. Impairment of vision was considered to have marked the onset in seventy-eight cases, gross hematuria in five and severe headaches alone in six. The average estimated duration of the malignant phase was 8.7 months, with a range of two weeks to six and one-half years. To check the reliability of these estimations, we also determined the average survival after the discovery of papilledema, which was 8.4 months, with a range of one day to seven years. In three instances, it was believed that the remission in the course of the disease was spontaneous.

Because of the importance of early treatment in patients with malignant hypertension, we tried to determine some sort of predictability of onset. In about one-fourth of the patients the onset was acute, in one-third the symptoms were of less than six months' duration, and in the remainder the complaints were long standing. The type of symptoms was similar in all three groups—headaches, congestive failure, gastrointestinal complaints, and the "fatigue complex." The suddenness and severity of onset appeared to be the distinguishing feature—the more sudden and severe the onset, the more likely a rapid progression into the malignant phase.

The significance of retinal changes in hypertension was reviewed. Subjective and objective changes in our patients were analyzed. Ninety per cent of our subjects complained of impairment of vision during the course of their illness. Papilledema, vascular changes and exudates were present in all at some time during the course; hemorrhages occurred in all but eight patients. Loss of vision and appearance of Keith-Wagener IV retinitis were closely correlated. Only three of fifteen patients who showed regression of Keith-Wagener IV retinitis did not receive specific treatment.

The effect of malignant hypertension on the heart was also reviewed. Three-fourths of our patients had symptoms of cardiac failure, while half had signs confirming its presence. Angina occurred in one-fifth of the group. Seventy-five per cent of the determinations of cardiac size by roentgenogram showed enlargement, while over 90 per cent of the electrocardiograms were abnormal. Seventy per cent of these electrocardiograms showed a pattern due to left ventricular hypertrophy. All patients who were examined at autopsy had enlarged hearts, the average weight being 527 grams. The heart is almost universally affected in the course of malignant hypertension.

The blood pressure levels in our group were as follows: the highest readings ranged from 300-160/180-100 mm. Hg; the lowest readings from 265-90/150-60 mm. Hg.

Changes in the central nervous system in malignant hypertension were also thoroughly studied, both as reported in the literature and as observed in our own group. Headaches were a complaint of 85 per cent of our patients, but neither in characteristics nor timing could they be considered definitive of malignant hypertension. Cerebrovascular disturbances were manifested in forty-four patients,

of whom twenty-five had "strokes." Convulsions occurred in eighteen patients, two-thirds of whom were dying in uremia. Lumbar punctures showed elevation of cerebrospinal fluid pressure, ranging as high as 500 mm. of water in 62 per cent of our patients. The therapeutic effectiveness of repeated spinal taps was estimated as beneficial in 22 per cent of our subjects, ineffective in 66 per cent, and harmful in 12 per cent. The spinal fluid protein content was increased in 69 per cent of the patients, in ten of whom the spinal fluid pressure was normal. Seventy-five per cent of our group showed some evidence of central nervous system damage.

The kidney is the organ most seriously involved in malignant hypertension. Eighty-four per cent of our patients had symptoms relating to the kidney, and all patients had some abnormality demonstrable by one or more laboratory tests. The significance of the symptoms has been analyzed.

Results of laboratory studies have been summarized and correlated with rate of survival and pathologic changes observed at autopsy. The impression that nephrosclerosis is the lesion most apt to occur when good renal function is retained in the presence of hypertension and Keith-Wagener IV retinitis was amply verified. In our series of patients the basic renal lesions found at post-mortem examination were nephrosclerosis in fourteen cases, glomerulonephritis in seven, and pyelonephritis in twelve.

A bleeding tendency developed in 57 per cent of our patients. Uremia was twice as common in this group as in the remaining patients. A moderate or severe anemia was present in half the group at the time when papilledema was discovered. When the hemoglobin was normal at the time malignant hypertension was diagnosed, nephrosclerosis was the most likely lesion.

Reports on the various forms of treatment applicable in malignant hypertension were mentioned, and the experience with their use in our group was presented briefly.

An increased survival time may be expected, provided vigorous therapy is supplied to hypertensive patients with papilledema (a) before renal function is impaired, and (b) before irreversible damage is done to cerebral vessels or to the heart.

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ELECTROCARDIOGRAPHIC CHANGES IN HYPERTENSION TREATED BY METHONIUM COMPOUNDS

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TREATMENT of arterial hypertension by means of the methonium compounds has been in progress for over two years.¹⁻⁵ Restall and Smirk¹ made use of the postural hypotension produced by these compounds to enhance the falls in blood pressure produced in hypertensive patients under treatment. Smirk and Alstad⁶ reported that effective control of blood pressure levels could be maintained in the great majority of hypertensive patients by subcutaneous injections of hexamethonium bromide (C₆) or pentamethonium bromide (C₅). They reported that methonium treatment led to a reversion of the abnormal electrocardiogram of hypertension in the direction of normality.

The electrocardiogram in hypertension has been frequently described.⁷⁻¹⁵ It does not differ significantly from that seen in other conditions associated with hypertrophy of the left ventricle, such as disease of the aortic valve. In leads which reflect left ventricular potentials, such as the left-sided precordial leads, Lead aV_L and usually standard Lead I, the changes which occur consist of tall wide R waves, with depression of the S-T interval and inversion of the T waves. Deep S waves, with elevation of the S-T interval and tall T waves, occur in leads reflecting the potentials from the right ventricle, that is, the right-sided precordial leads and sometimes Lead aV_F and standard Lead III. The changes in the right sided precordial leads would appear to be reciprocal in nature to those occurring in the leads from over the left ventricle, and are probably an expression of the same abnormality, the polarity being reversed.

In a report on the spontaneous evolution of the electrocardiogram of fifty hypertensive patients, Canabal and associates¹⁶ reported that over a follow-up period of at least five years 50 per cent became worse, 40 per cent were unchanged, and 10 per cent showed questionable to slight improvement. It is apparent from these figures that spontaneous improvement in the electrocardiogram is unusual, and that electrocardiographic changes become worse or remain constant in the great majority of patients. Hence serial electrocardiograms taken during the course of treatment afford a useful and objective guide to the effectiveness of blood pressure control which has been achieved by any particular form of therapy.

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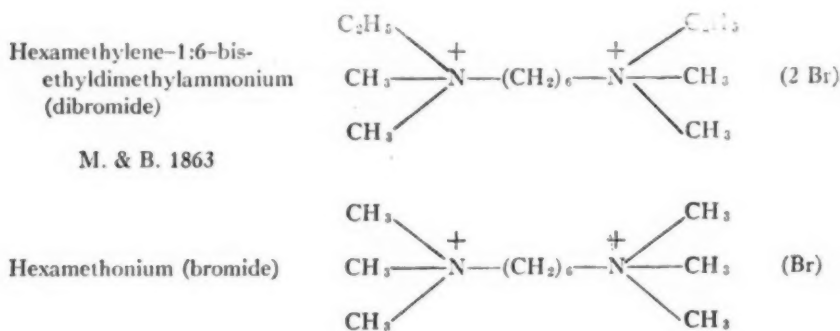
It should be emphasized that in this series of patients the methonium treatment has been administered and controlled in a way which ensures an effective degree of blood pressure reduction for a substantial part of the day. To do this entailed close supervision as well as frequent increase of dose to offset the development of drug toleration during the early months of treatment. It is unlikely that comparable results would be obtained from less exacting control over blood pressure levels.

The present paper is concerned with the changes which occur in the electrocardiogram following the effective treatment of arterial hypertension with hexamethonium bromide and homologous compounds, using the technique employed in this department.^{1,2,3,6}

METHODS AND SELECTION OF MATERIAL

Patients selected for treatment were all suffering from a considerable elevation of arterial blood pressure. Of a total of seventy-five patients included in this series, fifty-eight had essential hypertension, fifteen malignant hypertension, one was a diabetic with essential hypertension, and one had hypertension following toxemia of pregnancy.

All patients have been treated with the methonium compounds or similar substances. The great majority of patients have received repeated subcutaneous injections of hexamethonium bromide. A few patients obtained effective control of blood pressure by oral therapy with hexamethonium bitartrate. The remainder, a minority, were treated with subcutaneous injection of M. & B. 1863 which, as will be seen from the structural formula, is closely related to hexamethonium bromide. The pharmacologic effects of M. & B. 1863 do not appear to differ qualitatively from those of hexamethonium bromide.^{17,18}



Patients were not included in this report unless the following criteria were fulfilled:

1. The period of continuous treatment with one of the drugs described above was at least three months.
2. Serial electrocardiograms before and during treatment were available.
3. No digitalis had been administered.

All electrocardiograms were taken with the patient recumbent, and in almost all cases electrocardiograms from each patient were recorded on the same

machine. It has been found that when recordings are taken on different machines, quantitative differences in the voltage of the deflections occur, although the recordings are qualitatively similar. In all cases the leads recorded were the three standard bipolar limb leads, the augmented unipolar limb leads from the right arm (aV_R), left arm (aV_L) and left leg (aV_F),¹⁹ and the precordial unipolar leads from positions 1 to 6.^{20 21} Case numbers used correspond with those in earlier papers.¹⁻⁶ The electrocardiograms shown have been retouched for photography, and the originals have been submitted to the Editor

RESULTS

Two hundred and six electrocardiograms from seventy-five patients have been examined. The longest period of follow-up of any patient has been thirty months, and the shortest three months.

Grading of Electrocardiograms in Hypertension

Electrocardiograms have been divided into three grades as follows:

Grade I.—No definite abnormality.

Grade II.—(a) Slight depression of the S-T interval in Leads I, aV_L and V_6 , with flattening or negativity of the T wave of 0.5 mm. or less. (b) Considerable increase in voltage of the R wave in V_5 and of the S wave in V_2 , the sum of the two exceeding 30 mm. or the height of one exceeding 20 mm.

Grade III.—Considerable increase in voltages, together with advanced T-wave inversion and S-T interval depression.

Electrocardiogram Before Treatment

The gradings of the electrocardiograms taken before the onset of treatment are set out in Fig. 1, A.

Thirteen cases showed no definite electrocardiographic abnormality (17 per cent of the total). The remaining sixty-two cases showed evidence of left ventricular hypertrophy and strain. In twenty cases this was slight (Grade II) and in the remaining forty-two cases, which comprised 56 per cent of the total cases, the changes were advanced (Grade III).

QRS Changes.—

1. *Standard leads:* While left axis deviation has not been regarded as reliable evidence of left ventricular hypertrophy, this change was present in fifty-eight of the seventy-five cases. In the remaining seventeen patients the electrical axis of the heart was vertical. In patients showing other changes characteristic of left ventricular hypertrophy, the R wave in Lead I was usually tall with a deep S wave in Lead III, but nine of the seventeen patients showing no left axis deviation had other evidence of left ventricular hypertrophy.

2. *Precordial leads:* Abnormalities in the QRS complex in the electrocardiogram of hypertension consist of increase in voltage of the R waves from the left precordial leads, with reciprocal deepening of the S waves in the right-sided leads. We have examined the height of the R wave in Lead V_5 and the depth of the S wave in V_2 . These leads have been selected because they appear to be well clear of the transitional zone between predominantly positive and predominantly negative complexes, and because Leads V_1 and V_6 are usually much affected by rotation of the heart about the long axis where this is present. The sum of the S wave in Lead V_2 and the R wave in V_5 has been determined. In fifty cases this exceeded 30 millimeters. Forty-two of these fifty

cases had associated changes in the T waves which will be described below. In most of these patients the height of the R wave in V_3 or the depth of the S wave in V_2 exceeded 20 millimeters. In addition, the R wave in V_2 was usually diminutive or absent, while the S wave in V_3 was rarely present. In the whole series the average depth of the S wave in V_2 was 15 millimeters, while the average height of the R wave in V_3 was 17 millimeters. Three cases exhibited bundle branch block, in two the right bundle branch being affected and in one the left.

3. *Duration of QRS:* With the exception of the three cases showing bundle branch block, the duration of the QRS complex lay between 0.08 second and 0.1 second, with an average duration of 0.09 second.

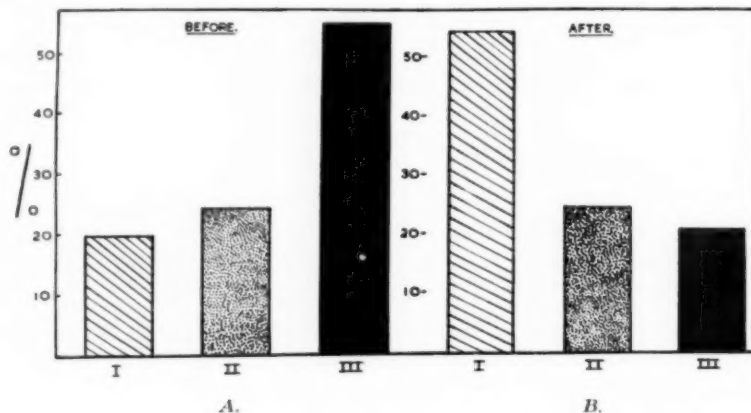


Fig. 1.—Distribution of cases in three grades: A. Before treatment; B. After treatment. For detail see text.

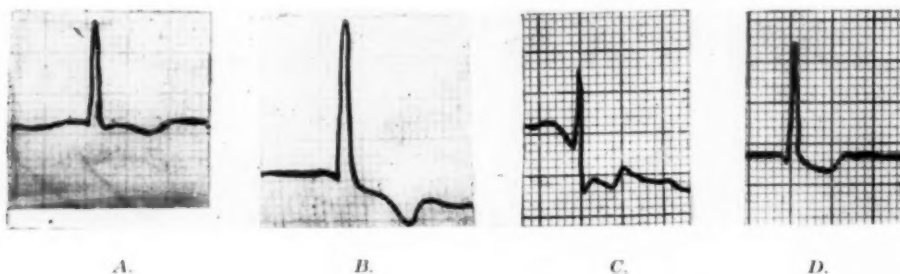


Fig. 2.—Typical changes of S-T segment and T wave in Lead V_6 .

A. Early hypertensive change showing "roller coaster T wave." B. Advanced hypertensive change. C. Myocardial ischemia. D. Digitalis effect.

S-T Interval and T-Wave Changes.—

1. *Standard leads:* The S-T interval and T-wave changes will be described together, since abnormalities of the former rarely occur without preceding changes in the latter. In the standard leads, the most characteristic changes occurred in Lead I and consisted of depression of the S-T segment with inversion of the T wave. This abnormality was seen in forty-four cases, and did not occur in the absence of similar changes in the left-sided precordial leads and in Lead aV_L , but it was absent in ten of the cases with precordial T-wave changes.

2. *Precordial leads:* The most characteristic changes occurred in the left-sided precordial leads, V_4 , V_5 and V_6 . The changes consisted of a curved depression of the S-T interval, with the convex surface upwards, often apparently continuous with the inverted T wave. The depression of the S-T segment differs in shape from that usually seen after digitalis administration (Fig. 2, D),

being convex upwards while the typical digitalis effect produces a sagging concave depression of the S-T interval. It differs also from the depression produced by subendocardial ischemia in coronary insufficiency, this condition characteristically producing depression of the S-T interval which is maximal at the beginning of the S-T interval (Fig. 2, C).

The T wave may be steeply inverted (Fig. 2, B) but is frequently diphasic with the negative phase occurring first, thus producing the characteristic "roller coaster" effect (Fig. 2, A). Characteristic S-T interval and T-wave changes occurred in Leads V_4 to V_6 in fifty-four cases, being advanced in forty-two. The maximal depression of the S-T interval below the isoelectric line in this series was 4 millimeters.

Reciprocal changes in the S-T interval and T waves occur in the leads taken from the right precordium, as described by Evans and associates.¹⁴ They consist of elevation of the S-T interval of up to 3 millimeters above the isoelectric line with a marked increase in the height of the T wave which may reach a voltage of 8 millimeters. These changes occur at the same stage as the development of S-T depression and T-wave inversion in Leads V_4 - V_6 and would appear to be reciprocal in nature.

The electrocardiographic changes seen in all patients are summarized in Table I.

TABLE I. ALTERATIONS OF THE GRADE OF SEVERITY OF ELECTROCARDIOGRAPHIC CHANGES IN HYPERTENSION BY METHONIUM TREATMENT

GRADE	TOTAL		ABNORMALITY	TOTAL ABNORMALITIES PRESENT	
	BEFORE TREATMENT	AFTER TREATMENT		BEFORE TREATMENT	AFTER TREATMENT
Grade I (Normal)	13	38		13	38
Grade II (Minor Abnormalities)	20	22	{ The sum of the R wave in V_5 and the S wave in V_2 greater than 30 mm. R in V_5 greater than 20 mm. S in V_2 greater than 20 mm. T wave inverted in Leads: I, V_5 , V_6 and aV_L I and aV_L alone V_5 and V_6 alone	8	6
				1	0
				4	3
				7	6
				0	4
		5	6		
Grade III (Major Abnormalities)	42	15	{ The sum of the R wave in V_5 and the S wave in V_2 greater than 30 mm. R in V_5 greater than 20 mm. S in V_2 greater than 20 mm. T wave inverted in Leads: I, aV_L , V_5 and V_6 I and aV_L alone V_5 and V_6 alone Right branch bundle block Left branch bundle block	42	12
				19	3
				25	8
				37	9
				0	0
				5	3
				2	2
				1	1

The Electrocardiogram Following Treatment

The changes which occur in the electrocardiogram of patients treated consist in almost all cases of a reversal of abnormal patterns, the electrocardiogram returning to normal in some cases. In only two cases deterioration was noted.

QRS Changes.—

1. *Standard leads:* In cases where the R wave was previously tall, diminution of size usually occurred. Left axis deviation when present was rarely reversed, but since it is probable that

changes in axis deviation are due in the main to variation in the electrical axis, which may be unassociated with hypertrophy of the ventricles, little significance can be attached to changes occurring in voltage of the QRS complex in the standard leads.

2. *Precordial leads:* The changes in voltage occurring in the QRS complexes in the precordial leads were striking in degree. Reduction in voltage of both the R wave in V_5 and the S wave in V_2 occurred in thirty-eight patients out of the fifty who had originally shown abnormally high voltages. In thirty-two of these thirty-eight cases, the voltage fell to within normal limits. In the remaining six the voltages, although decreased in amplitude, remained abnormally high by the standard previously described. Of the twelve cases which showed no reduction in voltage, nine showed no definite change while in the remaining three there was some increase in voltage. Of the three patients showing increased voltage after treatment, two concurrently showed improvement in T-wave changes; the remaining patient showed over all slight deterioration at the end of six months' treatment. In the whole series of seventy-five, improvement occurred in forty-nine, there was no change in twenty-two, and there was deterioration in four.

The average depth of the S wave in V_2 after treatment was 10 millimeters, a fall in voltage of 5 millimeters when compared with the average before treatment. The average height of the R wave in V_5 after treatment was 12 millimeters, a fall in voltage of 5 millimeters.

S-T Interval and T-Wave Changes.—

Changes occurring in the S-T interval and T-wave following treatment consisted of a return towards a normal pattern. S-T interval depression in V_4 , V_5 , and V_6 , and in Leads I and aV_L usually disappeared in the early stages of treatment, gradual reversion of the T wave towards normal occurred more slowly (Fig. 6).

Of the fifty-four patients showing S-T interval depression or T-wave inversion before treatment, twenty-six had returned to normal after treatment, twenty had improved but still showed some abnormality, seven had not changed, and the T waves in one were worse. In the remaining twenty-eight patients in whom no definite abnormality had been present there was usually no change. In one of these patients, the amplitude of the T waves in the left-sided precordial leads increased in voltage by 0.5 millimeters, while in another the T wave decreased by the same amount.

Changes in the right-sided precordial leads were also in the direction of normality, with a decrease in the voltage of the T wave in Lead V_2 and restoration of the previously elevated S-T interval to the isoelectric line.

Some of the electrocardiographic changes are shown in Fig. 3.

Changes in the Electrocardiogram as a Whole

Before treatment commenced, thirteen (17.3 per cent) patients showed no electrocardiographic abnormalities of sufficient degree to warrant a diagnosis of left ventricular hypertrophy, the remaining sixty-two (82.7 per cent) showing moderate to advanced changes. After treatment for periods ranging from three to thirty months, thirty-eight patients (51 per cent) had no definite electrocardiographic abnormality, while the remaining thirty-seven (49 per cent) still showed evidence of left ventricular hypertrophy, although in most cases these changes were less advanced than previously (Fig. 6). Thus, in twenty-five out of sixty-two cases electrocardiograms showed complete reversion to normal (Table I).

The over all electrocardiogram was considered to have improved in fifty-seven cases (76 per cent), to have remained unchanged in sixteen cases (21.3 per cent), and to have deteriorated in two cases (2.7 per cent) (Fig. 1, B).

Correlation of Improvement With Period of Treatment

As might be expected, improvement in the electrocardiogram increases with the length of time that treatment has been received (Fig. 4).

Of eighteen electrocardiograms taken within three months of commencing treatment, seven showed some improvement, nine showed no significant change, while two had deteriorated.

Of thirty-six electrocardiograms taken after three to six months' treatment, twenty-seven showed improvement, six no change, while three had deteriorated.

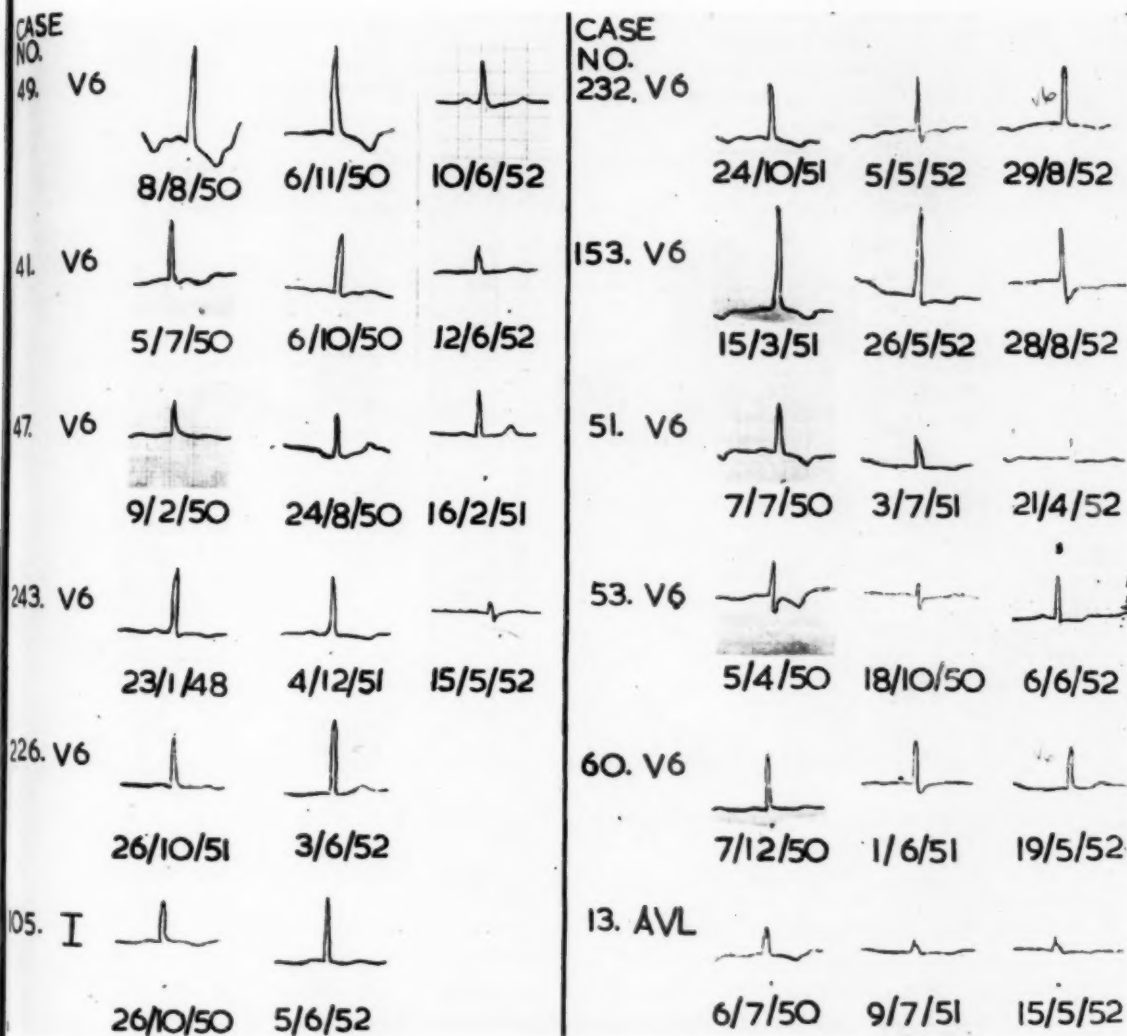


Fig. 3.—Some examples of improvement in the electrocardiogram from twelve of the seventy-five patients.

Of fifty-two electrocardiograms taken after six to twelve months' treatment, forty-six showed improvement while the remaining six showed no change. None had deteriorated as compared with the electrocardiogram taken before treatment.

Forty electrocardiograms were taken after treatment lasting twelve to thirty months. Thirty-five showed improvement, five being unaltered. All of the

electrocardiograms showing no improvement after one year had been normal before treatment commenced.

Thus all thirty-five patients with abnormal electrocardiograms before treatment who had been treated for one year or more had improved electrocardiograms. Of these, twenty-three were within normal limits while the remaining twelve were still abnormal, though to a lesser degree than initially.

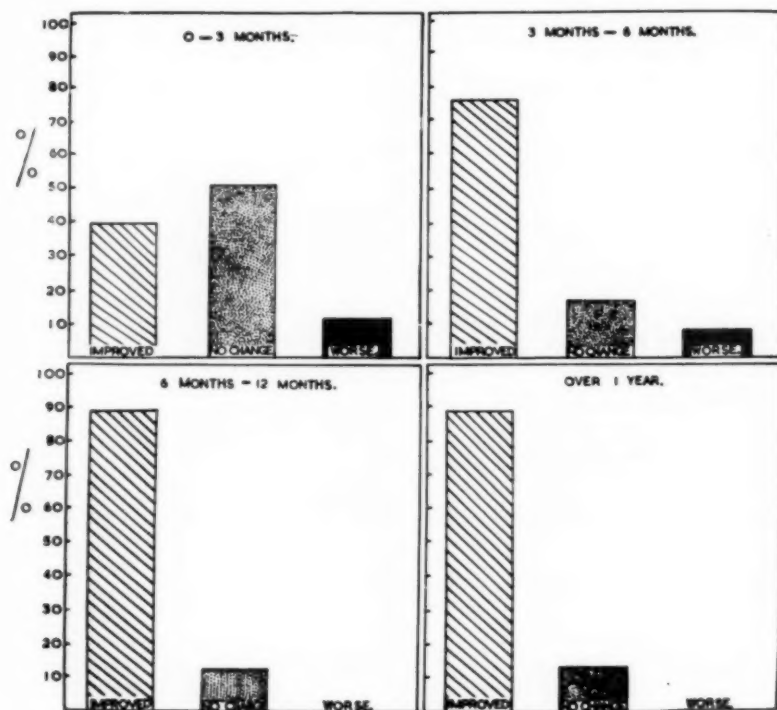


Fig. 4.—Progressive improvement with duration of treatment.

Correlation of Electrocardiographic Changes With Reduction of Blood Pressure

In all patients included in this series, the casual blood pressures were considerably raised before treatment was commenced, and in most the basal blood pressures were also high. Treatment was commenced under close supervision, recordings of the blood pressure at one-half hour intervals being made with the patients seated and standing. Doses were so adjusted that the systolic blood pressure in the standing posture reached about 120 to 135 mm. Hg in the trough of the blood pressure fall. After three weeks of such supervision, during which time the dose was raised daily to keep pace with the development of toleration, patients were seen at weekly or fortnightly intervals and the dose further raised as tolerance to the drugs progressed. The dose was maintained at such a level that slight faintness was experienced on standing still 1 hour after the drug had been taken. Occasional all-day tests were carried out as toleration to the drug

increased. It has been found that the casual blood pressures of patients attending the clinic, although considerably lower than those recorded before treatment commenced, were higher than the pressures recorded under test conditions. It is reasonable to assume that the blood pressures under home or working conditions lie between those recorded in the clinic and those recorded under test conditions.

The casual and basal blood pressures recorded before treatment are compared in Table II with the clinic and test blood pressures recorded at the last attendance. All the latter pressures were recorded in the standing position. The electrocardiographic changes for each patient are shown in the same Table.

Correlation With Clinical Features

A few of the cases in which the electrocardiogram improved are discussed in detail.

CASE 110.—A 45-year-old woman was first seen as an outpatient on Sept. 20, 1950, having had an attack of vertigo while making a bed.

On physical examination the blood pressure was found to be 270/140 mm. Hg. The apex beat was located in the fifth left intercostal space, three-fourths inch outside the mid-clavicular line, and there was a presystolic gallop rhythm present. The eye grounds were classified as Grade III, showing marked irregularity of the caliber of the arteries in both eyes, with extreme narrowing in places. There were a few flame-shaped hemorrhages in both eyes, with some recent soft exudate in the right eye. Neither disc showed any definite papilledema.

Teleroentgenograms revealed enlargement of the left ventricle, with no evidence of pulmonary congestion. An electrocardiogram (Fig. 5, A) showed a left ventricular strain pattern with inverted T waves in Leads I, aVL, V₃, and V₆.

Treatment with hexamethonium bromide was commenced on Oct. 13, 1950, and a good measure of blood pressure control was obtained, but the patient discontinued the injections in March, 1951, and did not attend again until February, 1952, shortly after she had had two paroxysms of nocturnal dyspnea.

Examination at this time revealed that the apex beat was now one inch outside the mid-clavicular line and the presystolic gallop rhythm was still present. The blood pressure was 240/140 mm. Hg. Further teleroentgenograms revealed no significant increase in the size of the heart shadow, but the electrocardiogram (Fig. 5, B) showed some advance in the left ventricular strain pattern. The eye grounds were unchanged.

Treatment was recommenced on March 2, 1952. Since that time she has had no recurrence of her nocturnal dyspnea. Further electrocardiograms (Fig. 5, C, D) taken in May, 1952, and June, 1952, showed a progressive regression of the changes previously present.

Thus, during a period of one year without treatment the clinical and electrocardiographic features had deteriorated. Within three months of recommencing treatment her condition was clinically improved and regression of electrocardiographic changes had commenced.

CASE 283.—A 54-year-old man was first seen on Mar. 28, 1952, following a thrombosis of the left retinal vein. He had had a headache for several months but was otherwise free of symptoms. The casual blood pressure was 250/140 mm. Hg. A teleroentgenogram of the chest showed moderate left ventricular enlargement and the eye grounds showed Grade II changes in the right, the condition of the left being obscured by the retinal vein thrombosis. The electrocardiogram (Fig. 6, A) showed a well-marked left ventricular hypertrophy and strain pattern.

He began treatment with hexamethonium bromide on April 22, 1952, and the electrocardiograms taken six weeks and three months after the beginning of treatment showed a progressive improvement (Fig. 6, B, C). His visual symptoms are unchanged by treatment.

CASE 123.—A 56-year-old man was admitted to the Dunedin Hospital on Dec. 20, 1950, complaining of failing eyesight and headache for some months.

TABLE II. BLOOD PRESSURES BEFORE AND AFTER TREATMENT, WITH ALTERATIONS OF THE GRADE OF SEVERITY OF ELECTROCARDIOGRAPHIC CHANGES

CASE NO.	BEFORE TREATMENT			DURATION OF TREATMENT IN MONTHS	AFTER TREATMENT			DIAGNOSIS†
	CASUAL BLOOD PRESSURE	BASAL BLOOD PRESSURE	ECG GRADE		CLINIC BLOOD PRESSURE* (mm. Hg)	TEST BLOOD PRESSURE* (mm. Hg)	ECG GRADE	
12	245/190	160/95	III	30	138/98	110/74	II	Diabetes
13	275/155	160/90	III	24	168/98	122/68	I	E.H.
14	230/122	178/114	III	25	158/98	130/90	I	E.H.
16	238/128	214/124	III	24	140/112	130/100	I	E.H.
17	250/130	190/114	II	26	138/88	124/78	I	E.H.
21	200/140	182/134	III	24	164/98	126/72	II	E.H.
25	254/140	190/102	III	5	174/118	128/98	III	L.B.B.B.
27	212/138	180/114	I	22	170/118	138/92	I	E.H. Sympathectomy
40	220/170	190/118	III	22	164/112	138/102	I	M.H.
41	242/135	190/110	III	24	168/108	126/88	I	M.H.
42	198/120	160/110	II	20	166/124	130/82	I	E.H.
47	196/124	194/144	III	19	174/112	130/90	I	E.H.
51	250/140	212/136	III	28	152/94	126/84	I	M.H.
49	262/132	182/106	III	24	142/88	118/72	I	M.H.
52	248/140	195/125	III	11	190/130	130/85	III	M.H.
53	265/152	220/120	III	26	148/88	130/85	I	M.H.
57	230/120	210/120	III	18	168/108	140/110	II	E.H.
59	210/130	188/128	III	11	172/112	146/98	III	E.H.
60	240/140	184/116	II	11	152/112	132/110	I	E.H.
65	240/140	158/110	III	17	164/106	132/90	I	E.H.
76	260/146	220/138	III	10	172/142	136/80	III	M.H.
82	208/112	132/94	I	18	158/116	122/86	I	E.H.
98	184/102	146/88	II	20	158/104	126/96	I	E.H.
100	224/150	216/148	II	20	156/122	132/96	I	E.H.
103	240/120	178/114	II	20	158/114	128/90	II	E.H.
105	258/138	160/132	III	20	182/104	120/98	II	E.H.
107	200/130	180/120	III	20	172/108	134/90	I	E.H.
109	238/142	148/100	I	18	168/128	120/98	I	E.H.
110	270/140	202/120	III	5†	152/94	132/98	II	E.H.
123	226/136	218/124	III	18	182/130	118/76	I	M.H.
124	232/124	192/116	III	19	168/118	126/82	II	E.H.
129	296/176	228/130	III	20	178/108	120/96	II	E.H.
134	230/180	180/132	III	14	148/98	118/112	III	E.H.
142	250/150	224/126	III	18	174/92	122/84	II	E.H., Left ventricular failure
152	210/140	170/100	I	16	162/130	132/88	I	E.H.
153	230/150	182/116	III	16	172/98	130/92	III	E.H.
159	250/170	220/130	III	10	222/132	130/94	II	M.H.
161	230/150	200/140	III	17	188/112	126/110	II	E.H.

	142	152	153	230/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
159	250/170	250/170	250/170	250/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
161	230/150	230/150	230/150	230/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
162	254/118	254/118	254/118	250/110	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
163	230/140	230/140	230/140	230/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
164	210/120	210/120	210/120	210/110	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
165	230/160	230/160	230/160	230/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
171	230/160	230/160	230/160	230/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
183	230/130	230/130	230/130	230/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
191	230/120	230/120	230/120	230/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
193	220/140	220/140	220/140	220/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
194	222/122	222/122	222/122	222/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
203	260/130	260/130	260/130	260/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
204	284/167	284/167	284/167	284/167	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
206	258/174	258/174	258/174	258/174	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
207	264/160	264/160	264/160	264/160	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
210	217/140	217/140	217/140	217/140	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
213	250/130	250/130	250/130	250/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
216	224/140	224/140	224/140	224/140	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
219	220/145	220/145	220/145	220/145	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
220	260/180	260/180	260/180	260/180	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
222	220/130	220/130	220/130	220/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
225	250/150	250/150	250/150	250/150	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
226	200/130	200/130	200/130	200/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
228	192/130	192/130	192/130	192/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
230	200/120	200/120	200/120	200/120	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
232	250/114	250/114	250/114	250/114	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
235	252/136	252/136	252/136	252/136	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
236	280/140	280/140	280/140	280/140	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
239	260/150	260/150	260/150	260/150	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
240	260/130	260/130	260/130	260/130	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
243	254/156	254/156	254/156	254/156	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
248	268/146	268/146	268/146	268/146	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
252	250/150	250/150	250/150	250/150	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
255	200/120	200/120	200/120	200/120	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
261	230/128	230/128	230/128	230/128	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
272	220/140	220/140	220/140	220/140	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
276	248/156	248/156	248/156	248/156	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
283	250/140	250/140	250/140	250/140	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure
288	240/120	240/120	240/120	240/120	210/140	236/150	224/120	170/100	182/116	III	16	174/92	162/130	132/88	130/92	II	E.H., Left ventricular failure

*"Clinic blood pressure" refers to the standing blood pressure at the last clinic attended, and "Test blood pressure" refers to the lowest blood pressure recorded in a standing position at the latest all-day test.

†E.H. = Essential Hypertension

M.H. = Malignant Hypertension

Post. Tox. H. = Hypertension following pregnancy toxemia

L.B.B.B. = Left Bundle Branch Block

R.B.B.B. = Right Bundle Branch Block

‡See text.

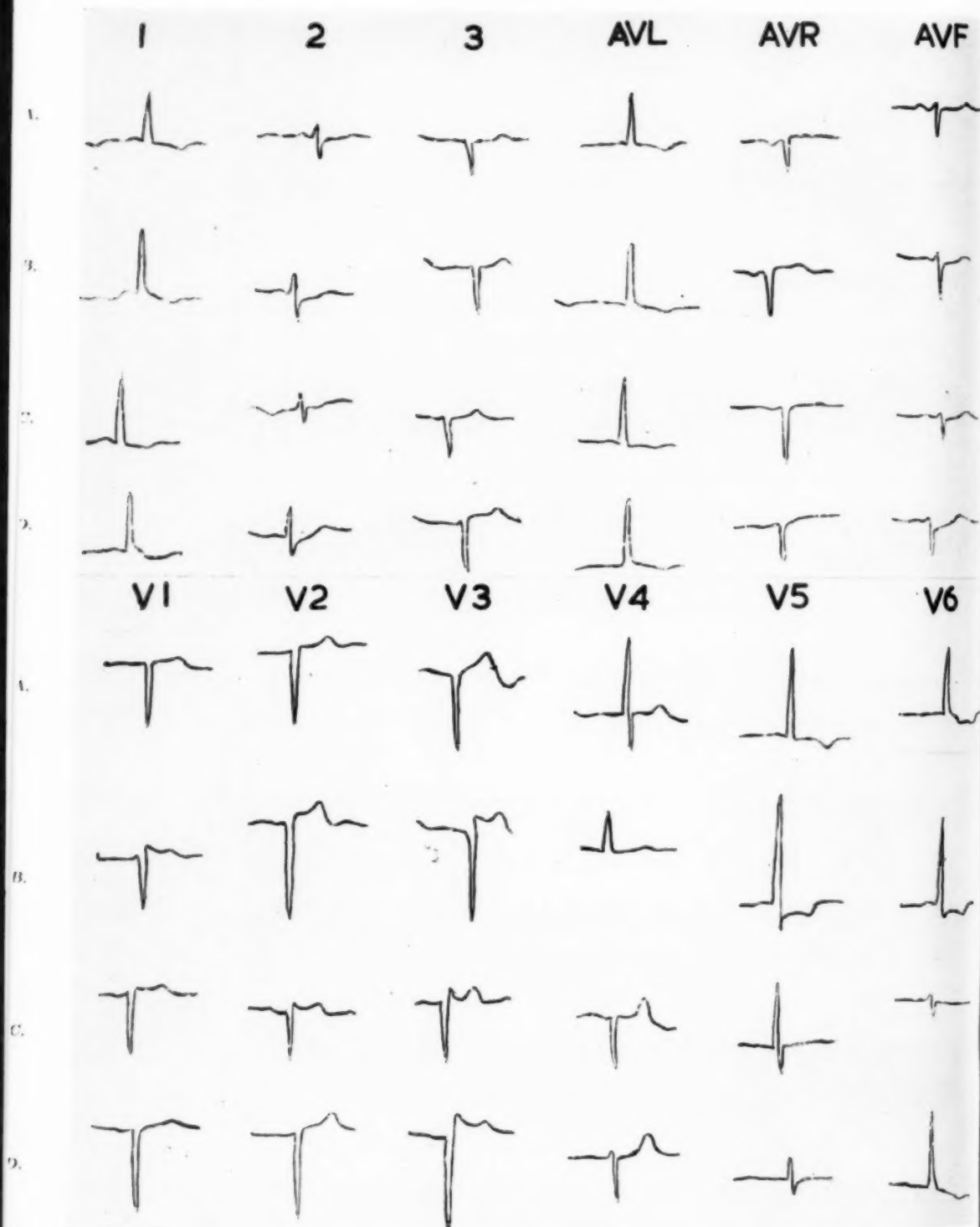


Fig. 5.—(Case 110.) A. September, 1959: Before treatment. Well-marked left ventricular strain pattern. Grade III. B. February, 1952: Eleven months without treatment. No change. Grade III. C. May, 1952: Two months' treatment. Marked improvement. Grade II. D. June, 1952: Three months' treatment. No further progress. Grade II.

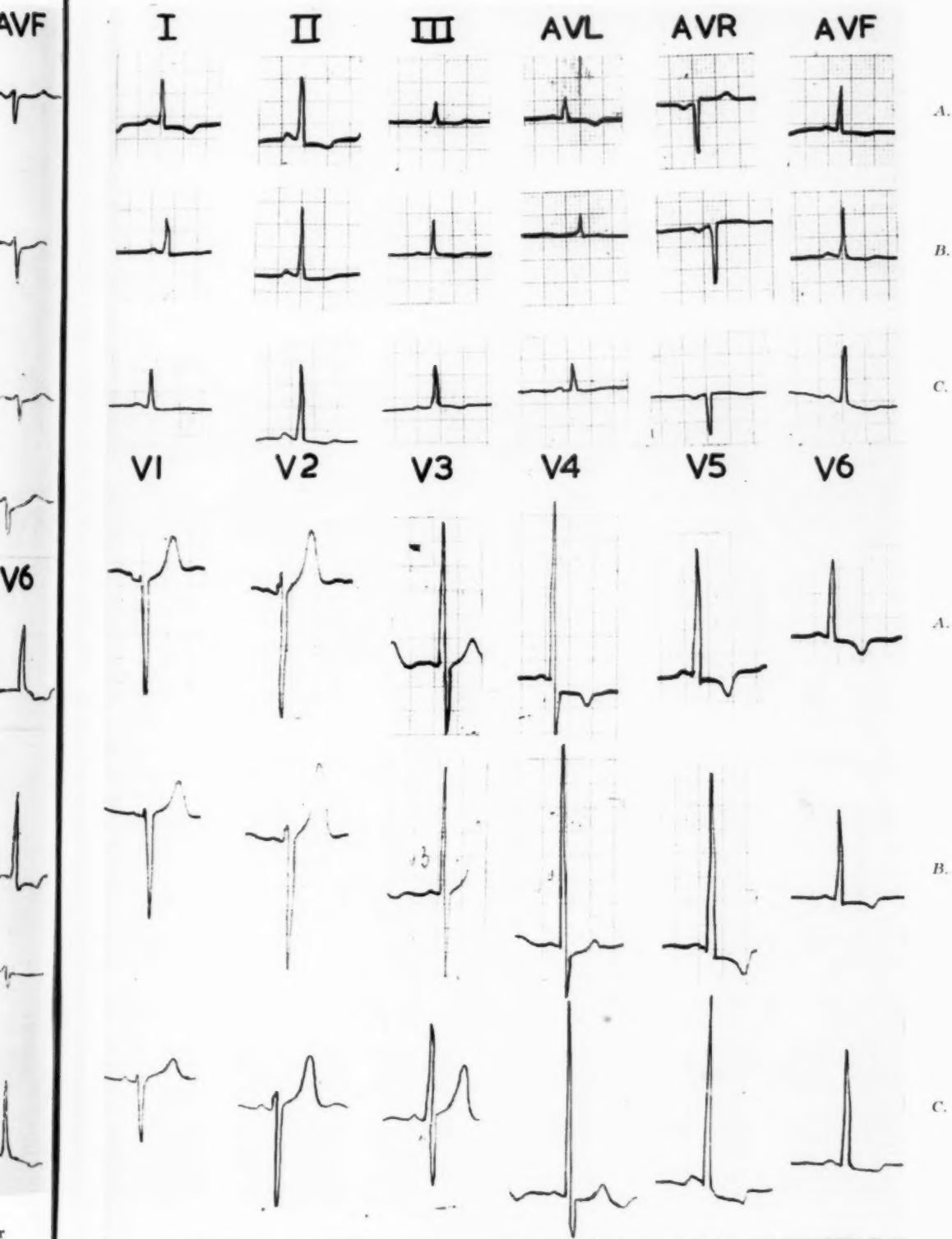


Fig. 6.—(Case 283.) A. March, 1952: Before treatment. Well-marked left ventricular strain pattern. No axis deviation. Grade III. B. May, 1952: Six weeks' treatment. Slight improvement. Grade III. C. July, 1952: Further improvement, but still Grade III.

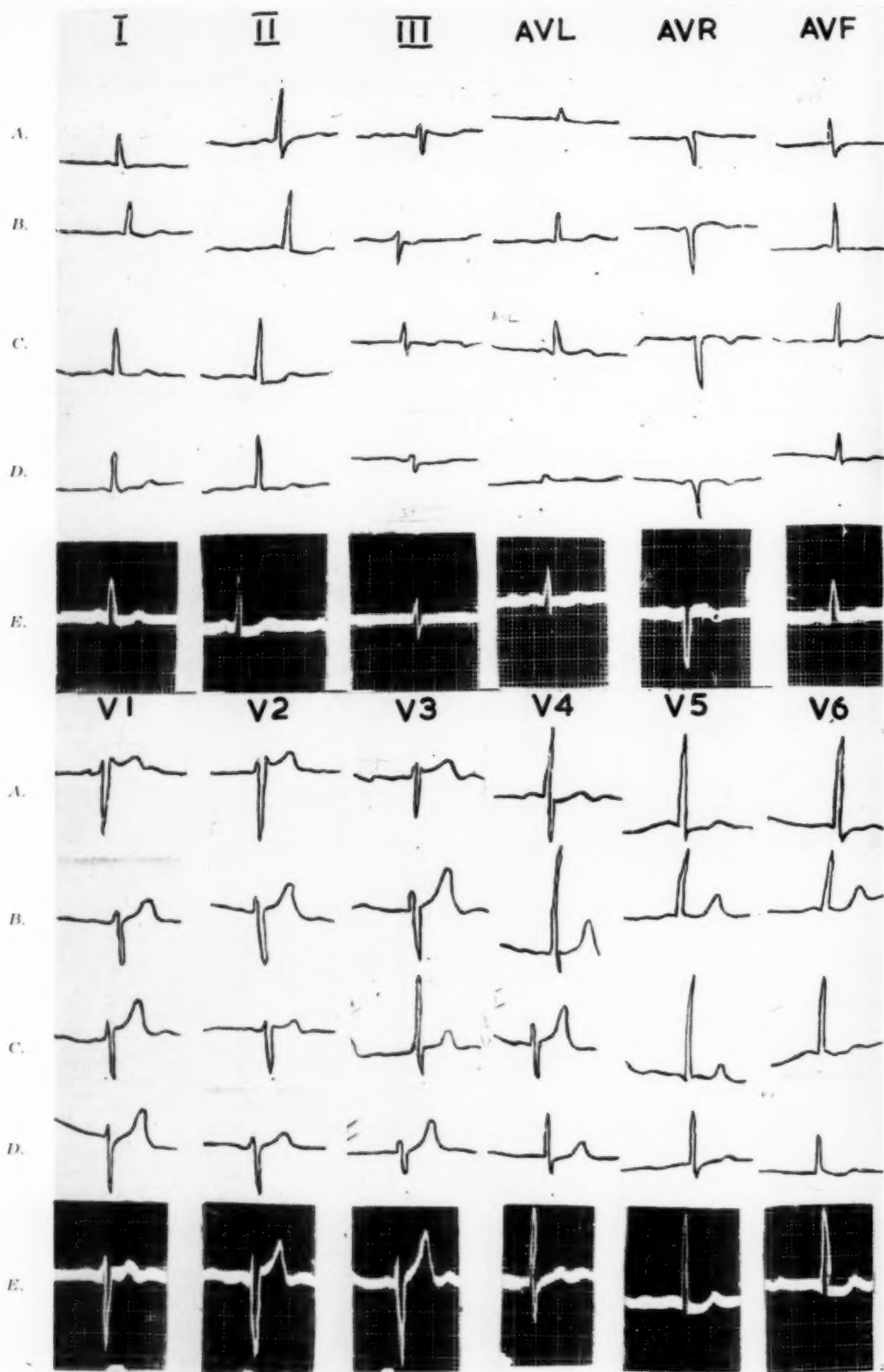


Fig. 7.—(Case 123.) A. January, 1951: Before treatment. Early left ventricular strain pattern. Grade II. B. February, 1951: Six weeks' treatment. T waves in V_5 and V_6 now normal. Grade I. C. May, 1951: No change. Grade I. D. July, 1951: Improvement maintained. Grade I. E. March, 1952: No abnormality. Grade I.

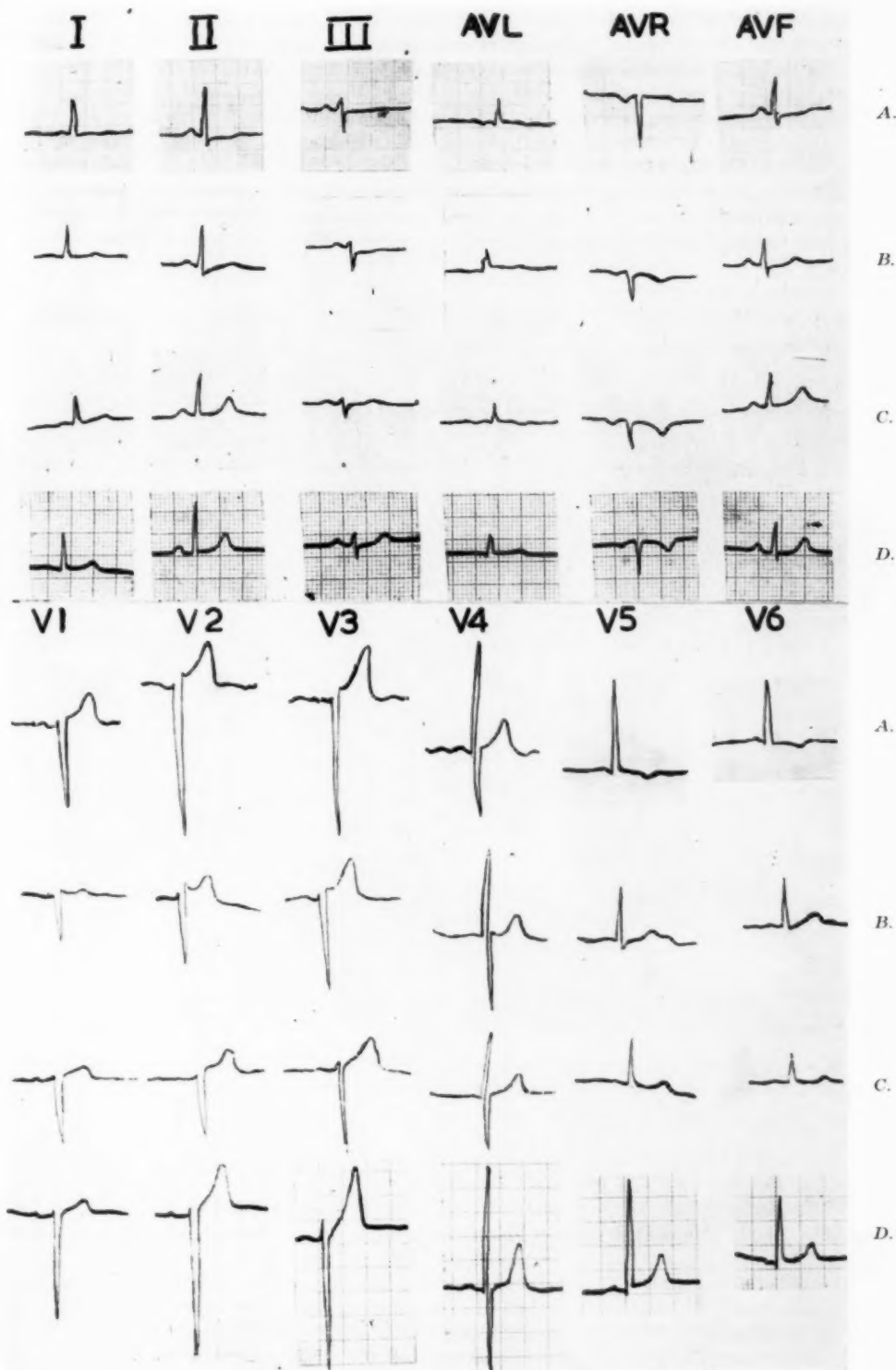


Fig. 8.—(Case 14.) A. April, 1950: Before treatment. Advanced left ventricular strain pattern, Grade III. B. November, 1950: Six months' treatment. Marked improvement, Grade I. C. October, 1951: Seventeen months' treatment. Improvement maintained, Grade I. D. May, 1952: Two years' treatment. No change, Grade I.

Physical examination revealed a casual blood pressure^{22,23} of 226/136 mm. Hg; there was some enlargement of the heart, both clinically and radiologically; and the eye grounds showed Grade IV changes with bilateral papilledema, hard exudate and a few hemorrhages, and soft exudate. Renal function was normal.

Treatment was commenced on Jan. 3, 1951, with hexamethonium bromide, and has been continued since. The electrocardiograms taken on this patient are shown in Fig. 7, and it will be noted that they show a substantial return to normal within three months, a follow-up record taken almost eighteen months after the beginning of therapy being quite normal.

When last seen in March, 1952, he was working full time as a business executive. The eye grounds showed no papilledema, hemorrhages, or exudate and he was free of symptoms.

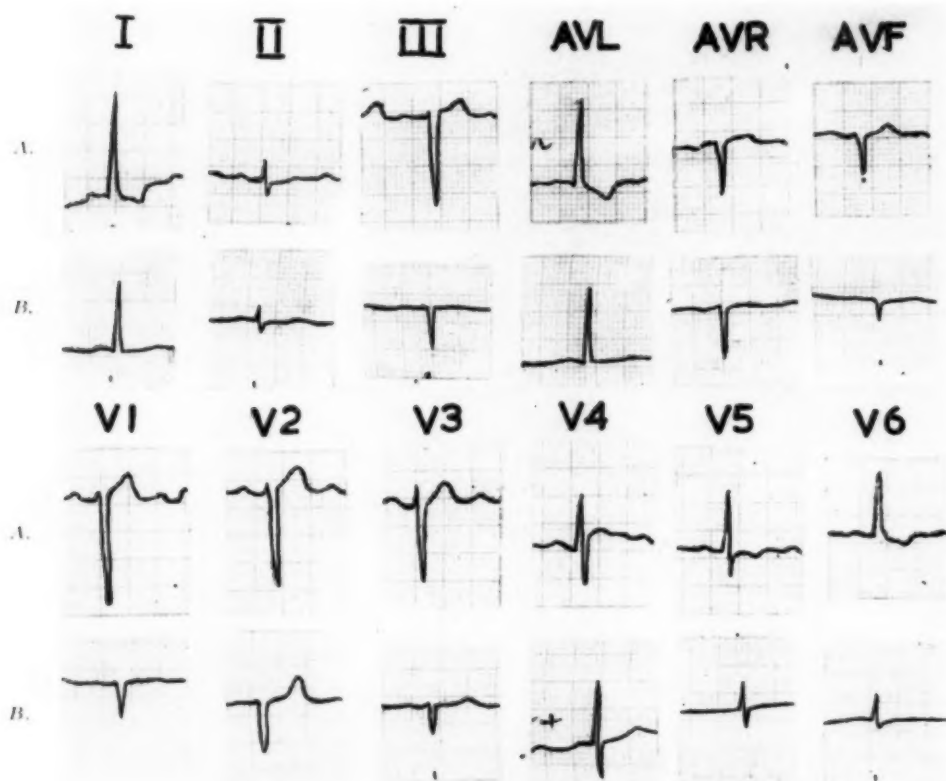


Fig. 9.—(Case 261.) A. December, 1951: Before treatment. Advanced left ventricular strain. Grade III. B. June, 1952: Two months' treatment. Marked improvement. Grade II.

CASE 14.—A 46-year-old man was first seen in April, 1950, complaining of headaches and dyspnea on exertion for about one year. Six months previously he had had a severe epistaxis.

On physical examination the casual blood pressure was 230/125 mm. Hg. The fundi showed Grade II changes. The electrocardiogram showed a well-marked left ventricular strain pattern (Fig. 8, A).

Treatment was commenced with hexamethonium bromide in May, 1950, and his symptoms were at once improved. Further electrocardiograms were taken in November, 1950, in October, 1951, and in May, 1952, and these showed a progressive improvement (Fig. 8, B, C, D). When last seen in August, 1952, he was at work and free of symptoms.

CASE 261.—A 57-year-old woman was first seen in December, 1951. She had been hypertensive for some years and had dyspnea on exertion and headaches for about two years. For about three months previously she had been having paroxysmal attacks of dyspnea at night.

On physical examination the blood pressure was 230/128 mm. Hg. There was slight left ventricular enlargement, confirmed radiologically. The eye grounds showed Grade II changes, and the electrocardiogram taken before treatment showed a well-marked left ventricular strain pattern (Fig. 9, A).

Treatment with hexamethonium bromide was commenced in March, 1952, and a further electrocardiogram taken two months later showed a striking improvement, with isoelectric S-T intervals and flat T waves (Fig. 9, B). When last seen in August, 1952, she was free of symptoms.

DISCUSSION

It has been shown that the continued controlled reduction of the arterial blood pressure which has been obtained by the administration of hexamethonium bromide or related compounds is associated with a progressive return of abnormal electrocardiographic changes toward normal. These results are comparable in type with observations on changes in the electrocardiogram in hypertensive patients following sympathectomy²⁴ or the rice diet.²⁵

The changes which have been described can only be due to a lessening of the load of the left ventricle due to a lowering of the arterial pressure. Spontaneous restoration of inverted T waves to normal may occur where these are due to pericarditis or to myocardial infarction, but spontaneous return of the inverted T waves associated with hypertrophy of the left ventricle due to hypertension must be rare. In the report of Canabal and associates¹⁶ previously quoted, slight spontaneous improvement in the electrocardiogram occurred in 10 per cent of the series, 50 per cent showing deterioration over a five-year period.

It is of interest to compare the electrocardiographic changes following methonium treatment with those following sympathectomy. White and associates²⁴ reported that 57.5 per cent of the electrocardiograms improved, 29.8 per cent remained unchanged, and 12.7 per cent deteriorated after sympathectomy. In the present series, 76 per cent were considered to have improved, 21.3 per cent to have remained unchanged, and 2.7 per cent to have deteriorated; the voltage in the precordial leads has diminished in the present series whereas little change in these leads was seen after sympathectomy. Furthermore, sympathectomy exerts its maximal effect on the blood pressure in the months immediately following operation, the extent of effective control declining rather than increasing with the length of time after operation²⁶ whereas, provided that the dosage of hexamethonium salts is increased as toleration progresses until a stable dose requirement is reached, the clinical and electrocardiographic improvement increases with length of treatment. It is clear therefore that in severe hypertensive patients the changes in the electrocardiogram after effective methonium treatment compare very favorably with lumbodorsal sympathectomy, and can be obtained without the risk which extensive surgical procedures must involve in patients of this type. Moreover, many of the patients in this series were unfit for surgery.

This study has been carried out by means of empirical interpretation of the electrocardiograms recorded. Speculation as to the nature of the mechanism of

changes of the QRS complex and T waves toward normal must necessarily be dependent on knowledge being available as to the factors producing the abnormalities concerned. If the characteristic changes are due to hypertrophy of left ventricular muscle, some correlation between heart size and electrocardiographic changes might be expected. In a review of the electrocardiograms of 218 hypertensive patients, Leishman¹⁵ found that 50 per cent of the hypertensive patients with major electrocardiographic abnormalities had normal-sized hearts, whereas 20 per cent with no electrocardiographic abnormalities had enlarged hearts. A similar lack of correlation between heart size and electrocardiographic changes was found by Evans and associates.¹⁴ Further, if patients with left ventricular failure, in whom cardiac dilatation may be assumed to be present, are excluded, regression of electrocardiographic abnormalities after treatment is not always associated with demonstrable reduction in heart size. Hence it cannot be assumed that return of the electrocardiogram to normal is necessarily due to involution of the hypertrophied muscle following control of blood pressure, although this seems to be the most probable explanation.

Leishman¹⁵ considers that the development of the characteristic changes of the strain pattern in hypertension is due to ischemia, in the case of large hearts, as a direct result of hypertrophy with a blood supply inadequate for the hypertrophied muscle, and in normal-sized hearts to defective coronary circulation. Pain of an anginal type is not a very frequent feature of hypertension, however, and Leishman finds the same incidence of electrocardiographic abnormalities in men as in women in spite of the greater prevalence of coronary ischemia in the male. Further, as has already been discussed, reversal of abnormal patterns is not always accompanied by reduction in cardiac silhouette.

Although the pathogenesis of the electrocardiogram of hypertension is at present obscure, most authors agree that the prognosis is worse in those patients with abnormal electrocardiograms than in similar hypertensive patients without electrocardiographic abnormalities. It is not unreasonable to assume that reversal of the abnormalities, where they are present, will be associated with an improvement in prognosis, especially when accompanied by relief of dyspnea and venous congestion.

SUMMARY

Serial electrocardiograms recorded before and after treatment with the methonium compounds in seventy-five patients suffering from arterial hypertension have been examined.

Electrocardiographic appearances consisting of S-T and T-wave changes and increased voltage in leads influenced mainly by the left ventricle improved progressively during the time that treatment was maintained, all abnormal electrocardiograms improving after treatment for a year or more.

Electrocardiograms from fifty-four patients with S-T or T-wave abnormalities showed a return to normal in twenty-six patients and a return toward normality in twenty.

Electrocardiograms from fifty patients with abnormally high QRS voltage showed a return to normal in thirty-two and a return in the direction of normal in six.

Improvements in the electrocardiogram appeared to be directly related to the degree of control of blood pressure achieved.

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THE ROLE OF PULMONARY STENOSIS IN THE PRODUCTION OF CHRONIC CYANOSIS

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THE GREAT interest in congenital heart disease which has developed in recent years is in part due to the dramatic relief of cyanosis which has been accomplished surgically in certain cases of morbus caeruleus. Most of the congenital malformations, in which a surgical correction of cyanosis has been possible, were found to be associated with pulmonary stenosis. In spite of the large amount of pathologic and physiologic data which have been collected from such cases the exact role of pulmonary stenosis in the production of chronic cyanosis is not yet well understood. In their earlier works Taussig and Blalock^{1,2} stressed the factor of "inadequate circulation to the lungs," caused by the obstruction of the pulmonary orifice, as the important factor in the production of cyanosis. While such an obstruction understandably produces cyanosis by promoting shunting of venous blood directly into the greater circulation through a coexistent intracardiac communication, the important question arises, whether an obstruction of the pulmonary outflow tract per se can cause cyanosis.

In previous communications^{3,4} it has been shown that cyanosis has been frequently reported in cases of pulmonary stenosis with patency of the foramen ovale, whereas it has been reported seldom in pulmonary stenosis with closed cardiac septa. The occurrence of anoxemia and chronic cyanosis, particularly when accompanied by polycythemia and clubbing of the digits, was proposed as the critical distinction between those cases of pulmonary stenosis with intact ventricular septum in which the foramen ovale was patent and those with closed foramen ovale. This interpretation has gained almost universal acceptance⁵⁻¹⁴ and experimental confirmation.^{15,16} However, Greene and associates,¹⁷ have collected from the literature sixty-eight autopsied cases of pure pulmonary stenosis ("unassociated with abnormal communication between the greater and lesser circulation") among which twenty-eight were reported as showing cyanosis. Furthermore, Dow and associates¹⁸ have suggested also that chronic cyanosis may exist with congenital heart disease in the absence of intracardiac shunts.

These implications that pulmonary stenosis may cause chronic cyanosis in the absence of abnormal intracardiac communications appear to contradict the widely accepted view that an intracardiac shunt is essential for the production of cyanosis in congenital heart disease. On account of the fundamental nature of the problem such a contradiction deserves a most careful scrutiny. It is the

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purpose of this paper to analyze the available clinical, physiologic, and pathologic data pertaining to the relationship of pulmonary stenosis to chronic cyanosis in an attempt to answer two questions: (1) Can pulmonary stenosis cause chronic cyanosis in the absence of intracardiac shunts? (2) What is the importance of pulmonary stenosis in the production of cyanosis in those cases in which it is associated with intracardiac communications? With a view to answering these questions three principal forms of pulmonary stenosis are reviewed: (a) pulmonary stenosis with closed cardiac septa; (b) pulmonary stenosis with intact ventricular septum and patent foramen ovale; and (c) the tetralogy of Fallot.

ANALYSIS OF DATA

A. *Pulmonary Stenosis With Closed Cardiac Septa*

The reports of sixty-nine autopsied cases of pulmonary stenosis with closed cardiac septa in the literature have been reviewed.* The ages of the patients at death varied from 5 months to 75 years. The following information was extracted, whenever available, from the reports: The presence or absence of cyanosis; clubbing of the digits; polycythemia; other essential clinical data, especially signs and duration of cardiac failure; cause of death; type and degree of pulmonary stenosis; presence and degree of right ventricular hypertrophy. Special attention has been given to statements regarding the foramen ovale.

In this series cyanosis was said to have been present in thirty-one cases. It was specifically stated that cyanosis was not present in twenty-one cases (Group I). It was not mentioned in seventeen cases. Of the cases in which cyanosis was not mentioned, three had no adequate clinical data; the remaining fourteen had sufficiently adequate clinical summaries to indicate that any appreciable degree of cyanosis would have been recorded, had it been present. These fourteen cases, therefore, also have been considered noncyanotic (Group II).

Cases in which cyanosis was reported have been divided into two groups: those in which it was considered questionable, or was recorded only as a terminal event (Group III, 15 cases); and those in which it was stated to have been of some severity and duration (Group IV, 16 cases).

It was reasoned that if cyanosis was due, directly or indirectly, to pulmonary stenosis, there should be some relationship between the degree of pulmonary stenosis and the presence of cyanosis. It was also considered to be of importance how many cases in each group died in chronic cardiac failure, which is, in itself, a factor in the production of cyanosis. Table I summarizes the information found regarding the relationship between the degree of pulmonary stenosis and the occurrence of cyanosis and indicates the number of cases in each group in which heart failure was the principal cause of death. It may be seen that in the group

*These sixty-nine cases included sixty of those reported by Greene and associates.¹⁷ (The cases of Elliotson; Cruveilhier; Carswell; d'Heilly; Genersich; Bret; Jossierand; and Currrens and associates, Case 2, were not included.) Five cases formerly reviewed by Selzer and associates³ (not listed by Greene and associates) were those of Eakin and Abbott (Case 1); Nabers; Leitmann; Graham; and Masserlot. In addition there were three cases reported by Allenby and Campbell⁵ (Cases GG, 1, and 2) and the one case of Hillman.¹⁹

with long-standing cyanosis there is the highest incidence of severe pulmonary stenosis and of cardiac failure. However, there is an appreciable number of cases in the noncyanotic Groups (I and II) in which severe pulmonary stenosis and chronic cardiac failure were present. The figures show that cyanosis is not frequent in cases of pulmonary stenosis and that it is not an essential feature of even the cases of most severe pulmonary stenosis accompanied by cardiac failure.

TABLE I. THE INCIDENCE AND SEVERITY OF PULMONARY STENOSIS AND OF HEART FAILURE IN REPORTED CASES OF PURE PULMONARY STENOSIS AND THEIR RELATION TO CYANOSIS

	NO. CASES	PULMONARY STENOSIS			DEATH DUE TO HEART FAILURE
		MILD	MODERATE	SEVERE	
NONCYANOTIC CASES					
Cyanosis reported as absent	21	3	6	4	4
Cyanosis not mentioned, but clinical data otherwise adequate	14	3	5	2	7
CYANOTIC CASES					
Cyanosis questionable, or reported as terminal event	15	4	6	2	9
Longstanding cyanosis reported as present	16	3	6	7	11

Of the sixty-nine cases of pure pulmonary stenosis the only ones in which unequivocal cyanosis was reported were the sixteen cases in Group IV. These reports were searched carefully for a common denominator that might explain the presence of cyanosis. In all of these cases, the degree of cyanosis was described as slight or moderate with two exceptions. In these two it was said to have been severe, in both instances during a terminal bout of cardiac failure. The duration of the cyanosis varied from a few months to several years before death. In the majority of cases it was of less than two years' duration. Polycythemia was recorded in three cases. Clubbing of the digits was reported in three cases and in one other it was questionable. In only one case²⁰ were both of these findings present. Of the eleven cases in which chronic cardiac failure was present, cyanosis developed at the time of the onset of failure in at least six. One other case, in which cyanosis may have preceded the onset of failure, was complicated by severe mitral stenosis of rheumatic origin.²¹

While all these cases were reported as "pure" pulmonary stenosis, in the sense defined above, a description of the foramen ovale was rarely given. In six cases it was not mentioned at all; in most of the others it was dismissed by inference with such statements as "fetal passages closed," or "no other anomalies."

The difficulty in assessing properly the role of the malformation in the pathogenesis of the cyanosis is illustrated by the following data from the best documented cases in which cyanosis was asserted to have occurred.

The case of Arnett and Long²² has been quoted in the literature repeatedly as a characteristic example of cyanosis appearing late in the course of pure pulmonary stenosis. The patient was a man 32 years old who died of carcinoma of the pancreas, without ever exhibiting important

cardiac symptoms. Two years before death he was noted to have developed patchy areas of bluish discoloration of the skin, but no cyanosis of mucous membranes or nailbeds was present. The arterial oxygen saturation was 94 per cent. At autopsy the heart was small (205 grams), and there was mild pulmonary stenosis (3.5 cm. in circumference), which was diagnosed as congenital. The right ventricle was not hypertrophied. The available data indicate that in this case there was (1) no anoxemia, (2) no significant degree of circulatory embarrassment due to pulmonary stenosis, and (3) no generalized peripheral cyanosis, since the usual areas of visibility of cyanosis were spared. The description of the patchy lesions suggests possibly localized areas of telangiectasis or localized vasomotor disturbances which perhaps bore no relationship to the valvular heart disease.

The only case of typical *morbus caeruleus* in the series, in which the triad of severe cyanosis, polycythemia, and clubbing of digits was present, was reported by Garrison and Feldt.²⁰ In this case the age of onset of cyanosis, the course, and the mode of death were strikingly similar to the events in cases of pulmonary stenosis with patent foramen ovale. For that reason it is regrettable that the authors did not include in their data a detailed description of the fossa ovalis.

Two other cases with polycythemia were that of Currens and associates,²³ Case 7 a 6-months-old infant who died of septicemia; and that of Allenby and Campbell,⁵ Case 2, a 26-year-old man who had had dyspnea and cyanosis since the age of 21 and obvious congestive heart failure for more than one year. Clubbing was apparent in the case of a 6-year-old girl who had heart failure and cyanosis for over a year, reported by Peacock,²¹ and in the case reported by Eakin and Abbott,²⁵ of an 11-year-old boy in whom cyanosis and heart failure developed seven months before death.

Comment.—The crucial point sought in this group of cases is whether pulmonary stenosis may cause cyanosis in the absence of an intracardiac shunt and, if so, the mechanism by which cyanosis is produced. In evaluating the evidence one must consider the relative reliability of clinical observations of cyanosis and the adequacy of pathologic descriptions to eliminate the possibility of a pathway for a shunt.

In evaluating the accuracy of clinical estimations of cyanosis one is seriously handicapped by the large subjective element in the perception of cyanosis. It has been shown that this may lead to completely conflicting judgments by a series of different observers of the same patient.²⁶ The large majority of the cases, on which the foregoing data are based, were reported prior to the time when supplementary circulatory studies were commonly made. Accordingly the cases reported as showing mild or questionable cyanosis, unsupported by observations of polycythemia, clubbing, or blood oxygen analyses, cannot be accorded the same weight as evidence on the question as those in which cyanosis was severe and unmistakable.

The implication of the designation "pure pulmonary stenosis" is that the case is not complicated by an intracardiac shunt. The occurrence of a shunt may be excluded only by the demonstration that no anatomic communication exists through which a shunt could occur. Until recently the emphasis has been upon the presence or absence of an interventricular septal defect. Whereas gross defects of the auricular septum probably have not been often overlooked, little attention has been given to the foramen ovale by a great many authors. A perfunctory inspection of the foramen, as carried out in routine pathologic examination, may lead to the erroneous conclusion that it is closed. The common occurrence of anatomic patency of the foramen in normal hearts has detracted from the

appreciation of its importance under special circumstances. Only a careful probing will reveal the patency in many instances. That an anatomic patency has been overlooked in some instances is a justifiable suspicion, especially in older cases. As example that this actually has happened in one case of this sort is provided in the article (Case 2) of Eakin and Abbott.²⁵ The original protocol is presented in which the foramen ovale was reported as closed. The heart was later examined by Abbott, and reported by her as an example of pulmonary stenosis with widely patent foramen ovale. For this reason it has been emphasized that in most cases the description of the fossa ovalis was not included. In such cases there is no certainty that an intracardiac shunt may not have been present.

The possibility that pure pulmonary stenosis may lead to anoxemia and cyanosis is implied by the view that "diminished circulation to the lungs" is an additional factor in the production of anoxemia operating independently of the veno-arterial shunt.¹ This view is not supported by direct evidence and the mechanism of cyanosis on this basis is obscure. The lowering of the oxygen saturation in the arterial blood can be caused by only one of two factors: (1) an admixture of venous blood with the oxygenated blood that has returned from the lungs, or (2) incomplete oxygenation of the blood in the lungs. The first factor, the shunt, is absent in pure pulmonary stenosis. The second, or pulmonary factor has never been proved to operate in congenital heart disease.²⁷ First of all, arterial anoxemia has never been demonstrated in any proved case of pure pulmonary stenosis that has been reported. Furthermore, in several cases of pulmonary stenosis associated with intracardiac shunts, the blood returning from the lungs has been shown to be fully oxygenated by catheterization of pulmonary veins²⁸ and by obtaining samples of pulmonary capillary blood.²⁹

The role of "increased deoxygenation" (Abbott) as a cause of cyanosis in pulmonary stenosis cannot be affirmed or denied on the basis of the information thus far available. It has been said above that in most cyanotic cases, the occurrence of cyanosis coincided with cardiac failure. However, the frequency of cardiac failure without cyanosis in cases of pure pulmonary stenosis does not lead one to believe that heart failure due to pulmonary stenosis is more frequently associated with cyanosis than is heart failure due to other causes. Similarly, the records do not give the impression that cyanosis, when present, is often more severe in these cases than in cases of heart failure of other origin.

In addition to the factor of heart failure one must consider the possibility that peripheral cyanosis might be due to a low oxygen content of the venous blood brought about by a low cardiac output wherein the tissue oxygen consumption is met largely by an increased arteriovenous oxygen difference. While this is a theoretical possibility, which might explain some of the reported cases of cyanosis without heart failure, it has not been shown to be true in those cases of pure pulmonary stenosis in which pertinent circulatory studies were performed. The cardiac output usually has been found to be on the lower side of normal, showing some increment on exercise.^{17,18} It appears that the high right ventricular pressure, which has been recorded as much as eight times the normal, compensates remarkably well for the impediment to the outflow from this chamber in maintaining the circulatory rate.

Nevertheless, it appears that cyanosis, when present, in pure pulmonary stenosis only can be explained as the stagnant or peripheral type. This is supported by the series of cases of Greene and associates¹⁷ and Dow and associates¹⁸ in which the diagnosis was established by catheterization of the heart and the arterial oxygen saturation was found consistently to be normal. Three such cases were thought to be cyanotic.¹⁸ This suggests the questions, how severe cyanosis due entirely to stasis may be, and whether low circulatory rate with attendant increased deoxygenation of the capillary blood may be a stimulus to the development of clubbing and polycythemia. A definite answer to these questions will have to await further studies. The fact that polycythemia quite regularly accompanies arterial anoxemia, but seldom develops in heart failure, creates a doubt that peripheral stasis may stimulate the bone marrow sufficiently to cause significant polycythemia.²⁷ These questions cannot be answered by analysis of the data in the series of cases presented here for the reasons that arterial oxygen determinations were not made in any of the cases which had severe cyanosis, polycythemia, or clubbing, and the pathologic descriptions were lacking in details to eliminate the possibility that a shunt existed.

In spite of the few unexplained exceptions noted, the collected data indicate unequivocally that pure pulmonary stenosis belongs to the noncyanotic group of congenital heart disease; the application of the term "cyanotic" to a type of congenital heart disease implies that the condition is a direct effect of the malformation and the consequent circulatory disturbance. This has not been satisfactorily established in any case of proved pure pulmonary stenosis.

B. *Pulmonary Stenosis With Patent Foramen Ovale**

This form of pulmonary stenosis is anatomically identical with pure pulmonary stenosis except for the fact that anatomic closure of the foramen ovale has not taken place. In all the case reports reviewed the interatrial communication consisted of a typical foramen ovale rather than a malformation of the atrial septum (persistent septum primum). Clinically, these cases stand in marked contrast to pure pulmonary stenosis in that severe cyanosis, polycythemia, and clubbing of the digits are characteristic features. The sizable series of cases of this syndrome diagnosed by cardiac catheterization,⁵⁻¹⁴ which have been reported in the last three years, indicate that this is one of the most common forms of *morbus caeruleus*.

Of the thirty-five autopsied cases† of this syndrome reviewed for this analysis, thirty were reported to have had cyanosis, and in fifteen it was described as severe. Comments on clubbing of the digits were available in eighteen cases; clubbing was present in fifteen, and absent in three. In fourteen cases the erythrocyte counts

*This term used in previous communications is retained in preference to other suggested terms such as, "pulmonary stenosis with interatrial septal defect" and "pulmonary stenosis with reversed interatrial shunt"³⁰ because: in all reported autopsied cases patencies of the foramina ovalia were found and not true developmental atrial defects; and in the majority of cases the valvulated foramen ovale permitted only a right-to-left shunt.

†The twenty-nine cases reported in the previous communication⁵ were supplemented by Case 2 of Eakin and Abbott,²⁶ cases 3, 4, 5, and 6 of Allenby and Campbell⁵ and the case of Josserand.³¹

or hemoglobin contents were given and they were elevated to polycythemic levels in thirteen. In eighteen cases the time of onset of cyanosis was recorded; it had been present since birth in two cases, had developed in infancy or childhood in nine, and in adolescence or adult life in seven cases. The influence of age on the statistics is important since three of the five noncyanotic patients died before the age of 16 years. The only adult who did not develop cyanosis was reported by Lafitte.³² Significantly, in this case the diameter of the foramen ovale was very small.

The relationship between the degree of cyanosis and the degree of pulmonary stenosis, as well as the size of the foramen ovale, has been tabulated for those cases over the age of 15 years, where such data were available. Table II shows that there is a direct relationship between cyanosis and the degree of pulmonary stenosis in this syndrome. An even closer relationship is shown in Table III between the size of the foramen ovale and the degree of cyanosis. These findings provide convincing evidence of the fact that the foramen ovale constitutes a pathway of veno-arterial shunt and that the volume of the shunt is related to both the size of this pathway and the degree of obstruction of the pulmonary outflow tract. The clinical-pathologic correlation is supplemented by oxygen saturation studies in six of the cases.* In one case the foramen ovale was only slightly patent and the arterial oxygen saturation was 90 per cent. In five others the foramen ovale was widely patent and severe anoxemia was recorded (arterial oxygen saturations of 70, 72, 78 and 79 per cent).

The clinical-pathologic evidence of shunt is supported by a large body of data gathered from numerous cases studied clinically in recent years,⁵⁻¹⁴ in which the final confirmation of the diagnosis by autopsy is not available. A reasonably certain diagnosis of pulmonary stenosis with patent foramen ovale can be made by means of cardiac catheterization. This has provided information regarding pressure relationships and the magnitude of systemic and pulmonary blood flows. It has been shown that the right ventricular systolic pressure reaches very high values, usually exceeding the systemic arterial pressure. The diastolic and right atrial pressures do not appear to be elevated until heart failure ensues. The mean pulmonary artery pressure is definitely lowered. The volume of blood shunted to the left atrium through the foramen ovale has been estimated to exceed one-half the volume of the caval venous blood returning to the right side of the heart in some cases.

Finally, the importance of the open foramen ovale is attested by the experimental demonstration of a right-to-left flow of blood through an artificial interatrial opening in the dog when pulmonary stenosis is also produced.¹⁶ Furthermore, it appears that such an opening acts as a "safety valve," permitting the right ventricle to withstand better the effects of constriction of the pulmonary artery.

The fact that no significant pressure differential between the auricles can be demonstrated until right ventricular failure occurs is not inconsistent with the

*Allenby and Campbell,⁵ Cases 3, 4, and 5; Joly and associates,⁷ Cases 1 and 2; Vandam and associates,³³ Case 4.

TABLE II. THE RELATION OF CYANOSIS TO THE DEGREE OF PULMONARY STENOSIS IN ADULT CASES WITH PATENCY OF THE FORAMEN OVALE*

DEGREE OF PULMONARY STENOSIS	CYANOSIS			
	NONE	SLIGHT	MODERATE	SEVERE
Slight	++	+	+	
Moderate			+++	++
Severe	+		+++	++++ ++++ ++

*Each case is shown by +.

observation that cyanosis and anoxemia usually precede the onset of failure by many years. Cardiac catheterization studies have demonstrated the fact that a large volume of blood can be shunted across an interatrial communication with a very small pressure gradient.

The delayed appearance of cyanosis noted in many cases of pulmonary stenosis with patent foramen ovale may be due to one of two factors: (1) The right-to-left shunt may actually be initiated late in life due to one of a variety of causes, such as an increase in degree of stenosis, widening of the foramen ovale due to stretching of a dilating right auricle, or to unknown factors governing filling of the right ventricle; (2) the shunt may be present early in life but the degree of anoxemia may be below the threshold of visible cyanosis until the ratio of shunt flow to pulmonary flow is increased by the various factors to the point where cyanosis becomes manifest. The results of pulmonary valvulotomy in cases of pulmonary stenosis with patency of the foramen ovale are in harmony with the concept of the pathogenesis of the cyanosis expressed above.³⁴⁻³⁶ The successful dilatation of the pulmonary valvular obstruction abolishes or markedly reduces the arterial anoxemia. Thus it is evident that the reduction of the high right intraventricular pressure may completely eliminate the right-to-left shunt through the foramen ovale.

TABLE III. THE RELATION OF CYANOSIS TO THE SIZE OF THE FORAMEN OVALE IN ADULT CASES OF PULMONARY STENOSIS WITH PATENCY OF THE FORAMEN OVALE*

SIZE OF THE FORAMEN OVALE	CYANOSIS			
	NONE	SLIGHT	MODERATE	SEVERE
Small	++	+	+	
Medium		++	+++	+++
Large			++	+++ +++ +++

*Each case marked by +.

C. Tetralogy of Fallot

In cases of this malformation, the relationship between the degree of cyanosis and the structural changes cannot be accounted for as simply as it has been in the preceding syndromes. The abnormalities affecting the course of the circulation that must be assessed are not only the degree of pulmonary stenosis and the presence of one or more intracardiac communications (interventricular and frequently interatrial) but also the degree of over-riding of the aorta. The latter is an important factor, which frequently is difficult to evaluate at post-mortem examination. Nevertheless, from an analysis of autopsied cases and from data afforded by cardiac catheterization certain pertinent deductions can be made.

An analysis of twenty-eight reported autopsied cases of the tetralogy of Fallot* has shown that there is no substantial difference in the age of onset or the degree of cyanosis between this group and cases of pulmonary stenosis with patent foramen ovale. At least four of the eighteen cases of tetralogy of Fallot, in which the age of onset of cyanosis was reported, had had no visible cyanosis until adolescence or adult life. About two-thirds of the cases were severely cyanotic during the terminal stage, whereas about one-half of the cases of pulmonary stenosis with patent foramen ovale showed a comparable degree of cyanosis. The range of the values of arterial oxygen saturation was similar in both groups.

All the evidence indicates that anoxemia in the tetralogy of Fallot is entirely due to an admixture of venous blood with the systemic arterial blood and that pulmonary oxygenation is unimpaired. Catheterization studies²⁸ have shown that in most cases the systolic pressure in the right ventricle equals that in the left ventricle; rarely, it is slightly lower. Thus, no significant right-to-left pressure gradient through the interventricular foramen has been demonstrated to support the assumption that the blood flows from the right to the left ventricle through the septal defect. Anoxemia is assumed to be due to one or both of the following factors: (1) turbulence and mixing of unoxygenated and oxygenated blood underneath the overriding aortic orifice; (2) a direct entry of venous blood into the aorta from the right ventricle in the cases of more pronounced dextroposition of the aorta.

It is noteworthy that, in spite of structural differences between the tetralogy of Fallot and the Eisenmenger complex, there is a marked similarity in the circulatory dynamics in these diseases. In the Eisenmenger complex the increased resistance which leads to elevation of the right ventricular pressure is in the pulmonary circulation instead of at the outflow tract of the ventricle itself. The obstruction to the flow at the pulmonary orifice is a more rigid one than that at the pulmonary arterioles; therefore the excess flow during stress and exercise are much more limited in the tetralogy of Fallot, and patients with the Eisenmenger complex can tolerate exercise better.²⁷

It has been postulated that a large defect of the ventricular septum (2 to 3 cm. in diameter) would provide a low-pressure outlet from the left ventricle which would deflect most of the output away from the systemic circulation unless the

*Selzer and associates,³ references 41 to 62.

resistance within the lesser circulation were elevated to a degree comparable to that on the systemic side.^{37,38} Therefore, with malformations which include a large ventricular septal defect, increased resistance within the right side of the heart, or the pulmonary circulation beyond it, is essential for the survival of the individual. Pathologic reports* indicate that the great majority of cases of the tetralogy of Fallot have large septal defects, and clinical reports show that the systolic pressures within the two ventricles and the aorta are, as a rule, equal.²⁸ Therefore, it may be concluded that pulmonary stenosis, which provides this increased resistance, may play an important part in maintaining life in the tetralogy of Fallot. On this account one can find serious theoretical objections to the performance of pulmonary valvulotomy^{33,39,40} in cases of the tetralogy of Fallot. It is the widely accepted view³⁷ that the pulmonary stenosis in these cases constitutes a fixed resistance, while the systemic arterioles provide a variable resistance, determining the relative systemic and pulmonary flows at any given time. Thus, pulmonary stenosis is an important barrier limiting the quantity of blood which can reach the lungs for oxygenation. In this respect it is a disadvantage. However, it is suggested, in view of the foregoing considerations, that this disadvantage is balanced by the advantage that pulmonary stenosis offers as a protection against the draining of most of the blood from the left ventricle into a "low pressure hole." Theoretically an optimal degree of reduction in the stenosis may be attainable, by means of which some improvement in pulmonary blood flow is realized without an undesirable sacrifice of the systemic flow. However, there is most likely a critical point beyond which the pulmonary orifice cannot safely be dilated. Further dilatation would throw the burden of maintaining the systemic flow upon the peripheral resistance in the pulmonary circuit. If this "second line of defense" became effective, then the tetralogy of Fallot would become converted into an Eisenmenger complex in all essential respects. Should, however, the peripheral pulmonary resistance prove inadequate in such a case, then life could not be maintained. No hemodynamic studies have been reported up to this time on patients with the tetralogy of Fallot, in whom valvulotomy has been performed, to afford a comparative evaluation of the benefits and dangers of this procedure.

DISCUSSION

The foregoing analysis of clinical, pathologic and physiologic observations in syndromes in which pulmonary stenosis plays an important part shows that there is a fundamental difference between pure pulmonary stenosis and that associated with intracardiac shunts. Pulmonary stenosis with closed septa constitutes an obstruction to the path of the circulation which is similar to that in acquired valvular disease, such as aortic stenosis. The ventricle proximal to the stenosis overcomes the increased resistance by a rise in pressure. In spite of the obstruction, however, the minute volume of flow in the systemic and pulmonary circulations is identical, as all the blood has to pass through the obstructed orifice.

*Selzer and Laqueur,³⁸ Table II.

Since no impairment of pulmonary oxygenation occurs and no shunting of blood is possible, the systemic arterial blood is completely saturated not only under basal conditions but also during exercise. Thus central (anoxemic) cyanosis cannot be demonstrated in pure pulmonary stenosis. Peripheral (stagnant) cyanosis has been reported to occur in pure pulmonary stenosis, but it has been pointed out that it probably depends on the presence of cardiac failure and may not be distinguished from the cyanosis associated with heart failure due to other forms of cardiac disease.

However, if pulmonary stenosis is associated with a communication between the two sides of the heart, the situation becomes immensely complicated. Proximal to the obstruction the blood is provided with an alternate route which it may take in part, dynamic conditions permitting. The direct entry of deoxygenated venous blood into the systemic arterial circulation creates anoxemia and anoxemic cyanosis. The peripheral arterial blood consists then of a mixture of fully saturated pulmonary venous blood and a partially unsaturated caval fraction. The oxygen saturation of this mixture is lowered in proportion to the quantity and the degree of unsaturation of the shunted caval fraction, which can be expressed by the following equation:

$$O_a = \frac{V_c \times O_c + V_{pv} \times O_{pv}}{V_c + V_{pv}}$$

(O_a = oxygen saturation of peripheral arterial blood; V_c = volume of the shunted caval fraction; O_c = oxygen saturation of caval venous blood; V_{pv} = volume of the pulmonary venous fraction; O_{pv} = oxygen saturation of the pulmonary venous blood)

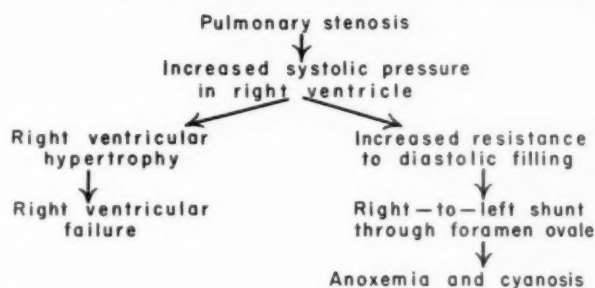
Whereas in a general way one can state that pulmonary stenosis facilitates, or even causes a right-to-left shunt through available intracardiac communications, its role appears to be quite different in cases with patency of the foramen ovale than it is in the tetralogy of Fallot. In pulmonary stenosis with patent foramen ovale the veno-arterial shunt leading to anoxemia and cyanosis is directly attributable to pulmonary stenosis which causes increased resistance to diastolic filling of the right ventricle and may reverse the normal interatrial pressure gradient and force open a functionally closed foramen ovale. On the other hand, pulmonary stenosis in the tetralogy of Fallot is thought to play the role of a necessary defense mechanism, permitting an adequate systemic output to be maintained in the presence of a large ventricular septal defect. A diagrammatic scheme of the factors leading to anoxemia and cyanosis in these two syndromes is presented in Fig. 1.

These considerations are of definite practical importance in connection with the surgical approach to correction of cyanosis and anoxemia. In pulmonary stenosis with patent foramen ovale excellent results from pulmonary valvulotomy are reported. When successful in reducing the right ventricular pressure, this operation eliminates or reduces the shunt. In the tetralogy of Fallot, the reduction of the degree of stenosis by either valvulotomy or infundibular resection should be approached with considerable caution, since the resistance within the

right ventricle probably cannot be lowered in such cases below a certain critical point without leading to disaster.

The older method of surgical correction of anoxemia in the tetralogy of Fallot, that of Blalock or Potts anastomosis, appears to be a much safer approach to the problem, but it represents a purely palliative procedure which does not aim at the correction of the cause of anoxemia.

PULMONARY STENOSIS WITH PATENT FORAMEN OVALE



TETRALOGY OF FALLOT

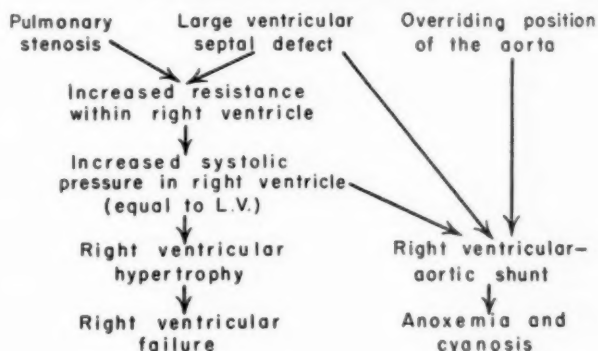


Fig. 1.—Interrelationship of factors in two types of pulmonary stenosis with intracardiac shunts.

SUMMARY AND CONCLUSIONS

The importance of pulmonary stenosis in the production of chronic anoxemia and cyanosis has been studied by an analysis of reported pathologic, physiologic and clinical observations.

Pulmonary stenosis not associated with an intracardiac communication is a noncyanotic disease. Determinations of oxygen saturation of arterial blood in such cases have shown normal values uniformly. Sixty-nine reported autopsied cases of pure pulmonary stenosis were carefully reviewed. It was noted, that while cyanosis was frequently mentioned in them, it was almost always associated with chronic cardiac failure. No relationship was found between the presence

and severity of cyanosis and the degree of pulmonary stenosis such as one would expect if the two had a causal relationship to each other. It is concluded that anoxemia is not a feature of pure pulmonary stenosis and that stagnant cyanosis, if present, is probably related to heart failure and not directly attributable to pulmonary stenosis.

In pulmonary stenosis with patent foramen ovale anoxemia and chronic cyanosis are almost always present and are due to a right-to-left shunt through the foramen ovale, which is caused by pressure changes resulting from the pulmonary stenosis. This is attested by the direct relationship between the degree of pulmonary stenosis and the severity of cyanosis on the one hand and by the similarly close relationship between the size of the foramen ovale and the cyanosis, on the other hand. Furthermore, catheterization data, angiocardiographic reports, and experimental studies provide a full support of this concept. The right-to-left shunt through the foramen ovale can be lessened or abolished by pulmonary valvulotomy.

In the tetralogy of Fallot with a large ventricular septal defect the systemic circulation must be supported by an elevated resistance within the lesser circulation as a condition for survival. Pulmonary stenosis constitutes one of the available mechanisms for this adjustment, and is not the only important factor in the production of anoxemia and cyanosis.

The different roles of pulmonary stenosis in its various forms in the production of chronic cyanosis are discussed in the light of possible surgical correction of pulmonary stenosis.

It is concluded that in the three syndromes analyzed here the pulmonary stenosis can be regarded as the principal factor responsible for chronic cyanosis only in the syndrome of pulmonary stenosis with patent foramen ovale.

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ABERRANT VENTRICULAR CONDUCTION SIMULATING PAROXYSMAL VENTRICULAR TACHYCARDIA

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THE INTELLIGENT management of a cardiac arrhythmia usually demands precise diagnosis in order that treatment may be effective. Although several excellent articles on aberrant ventricular conduction^{1,2} have appeared in the past few years, it is felt that this abnormality is not widely enough recognized and that confusion with paroxysmal ventricular tachycardia is particularly likely to occur, a point of some clinical importance. Langendorf³ states that as a rule digitalis should not be administered in the presence of ventricular tachycardia, but on the other hand, is often the drug of choice in the supraventricular tachycardias.

We recently have found several examples in our hospital of auricular fibrillation or tachycardia with aberrant ventricular conduction simulating paroxysmal ventricular tachycardia. On superficial analysis these were thought to represent ventricular tachycardias which did not respond to average doses of quinidine, but when the true nature of the arrhythmia was recognized, there was good response to adequate doses of digitalis. Special emphasis should be laid on Case 2, since this example was detected during a cardiac operation. With recent advances in technique and a larger number of centers participating in cardiac surgery during which constant electrocardiographic and oscillographic recordings are being utilized, prompt recognition of arrhythmias during operation is often essential so that improper treatment will be avoided.

CASE REPORTS

CASE 1.—A 37-year-old white man, a student, was admitted to the Fort Logan Veterans Administration Hospital on Nov. 4, 1949, complaining of recurrent episodes of palpitation associated with nervousness, sweating, and weakness for five days prior to admission. Physical examination revealed an obese white man, 72 inches in height, weighing 215 pounds. He was markedly apprehensive. The blood pressure was 115/85 mm. Hg. Heart size was not accurately delineated and the rate changed intermittently during examination from a slow regular rhythm of about 80 per minute to one of a rapid regular rhythm of about 180 per minute. During the attacks marked weakness, sweating, and fall of blood pressure to a range of about 80/70 mm. Hg was noted. The attacks of rapid rate could be aborted by left carotid sinus pressure, and appeared to be

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initiated by any sudden motion of the head. Such episodes of tachycardia were noted many times during the day and night. On one occasion, after an episode of several hours duration with hypotension, some sweating, and dyspnea, the patient was noted to be developing basal pulmonary râles and a protodiastolic gallop rhythm.

Initially he was given quinidine 0.2 Gm. every two hours for five days with no effect on the frequency of his tachycardia. The following day he was given quinidine 0.4 Gm. every four hours, day and night with no effect on the frequency; the only effect resulted from manual carotid sinus pressure which was effective in terminating an attack.

By the following day it was noted that the patient was in congestive heart failure indicated by cardiac enlargement, protodiastolic rhythm, and pulmonary basal râles. Consequently he was given digitoxin in the course of twelve hours and at this time there was noted to be a marked reduction in the frequency and duration of episodes of tachycardia with prompt elimination of his congestive heart failure. Later with continuation of digitoxin therapy complete freedom from further attacks was obtained (Fig. 1).

The figure shown is the admission electrocardiogram. Fig. 1, A (Lead I) shows auricular premature systoles with coupling. The first and second premature systoles show aberration of the right bundle branch type with prolonged QRS duration 0.12 second. Fig. 1, B (Lead II) shows a run of bizarre regularly spaced QRS complexes (rate 187) which were presumed to be a ventricular tachycardia but after review was considered to be a paroxysmal supraventricular tachycardia with aberrant ventricular conduction. Fig. 1, C (Lead II) shows a run of supraventricular paroxysmal tachycardia (rate 167) probably from a different auricular focus with only slight aberrancy, terminated by a long postsystolic pause.

Comment.—This patient represents a case of a functional cardiac disorder with paroxysmal supraventricular tachycardia which did not respond to the usual dosage of quinidine but dramatically responded to adequate digitalization. The tracing in Fig. 1, A clearly shows aberration following conducted auricular premature systoles. Only slight aberration is noted when a paroxysm of supraventricular tachycardia with a rate of 167 is registered as in Fig. 1, C, but pronounced aberration is noted when a paroxysm of supraventricular tachycardia, presumably from a different focus with a rate of 187 is registered as in Fig. 1, B. With the more rapid rate, the affected branch bundle is probably unable to recover sufficiently to conduct the succeeding impulse; whereas, when the rate is relatively slower at least partial recovery occurs in this branch bundle.

CASE 2.—A 35-year-old truck driver was admitted to the Fort Logan Veterans Administration Hospital on May 7, 1951, as a transfer from another hospital, complaining of abdominal swelling and weakness. He had entered that hospital in early 1948 with an illness characterized by chills, fever, easy fatigability, shortness of breath on exertion, and transitory migrating arthropathy. This was followed by congestive heart failure which was recurrent and necessitated six subsequent admissions to hospital. Since his condition was progressive and becoming intractable, he was transferred to this hospital. Physical examination revealed a chronically ill man with massive anasarca, distended neck veins, and enlarged pulsating liver. Blood pressure was 110/100 mm. Hg. A pronounced paradoxical pulse was noted. Cardiac examination revealed enlargement to the left and right. The rhythm was grossly irregular and an electrocardiogram revealed auricular fibrillation. The pulmonic second sound was markedly accentuated and split. A faint low-pitched apical diastolic murmur was heard. On June 12, 1951, he underwent cardiac catheterization. The results of this examination were felt to be in keeping with a diagnosis of chronic constrictive pericarditis, and this coupled with the clinical suspicion was felt to warrant exploratory thoracotomy with pericardiectomy. This operation was carried out on June 25, 1951, by Dr. Robert K. Brown under Pentothal Sodium induction with cyclopropane anesthesia. Throughout the operation frequent intermittent electrocardiographic recordings were taken with a direct writing instrument.

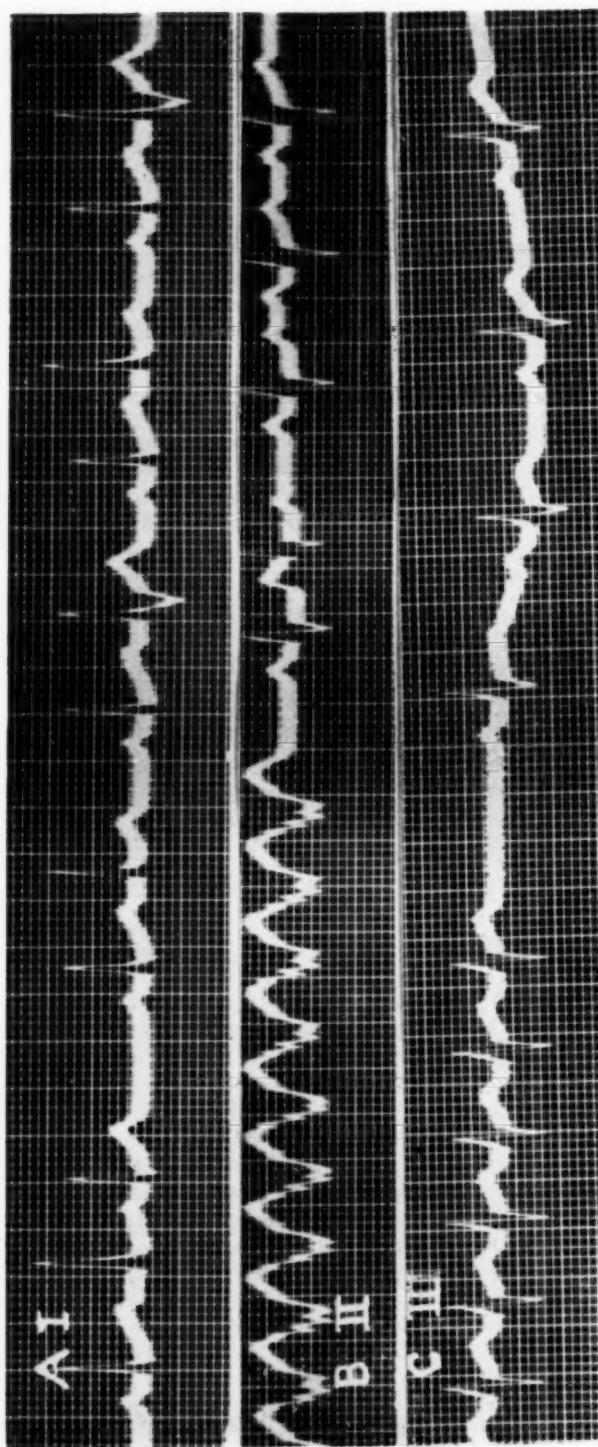


Fig. 1.—Discussed in text. From Veterans Administration Hospital, Boise, Idaho, M.I.L. File No. 1539.

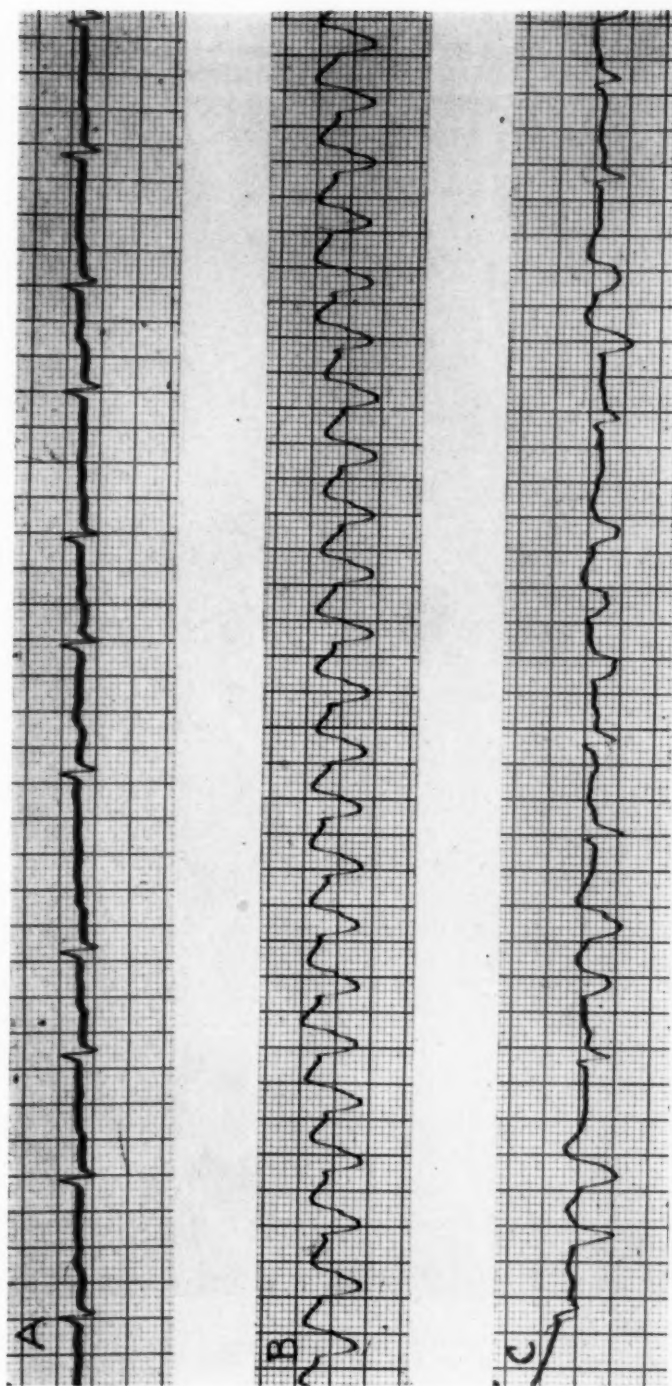


Fig. 2.—Discussed in text. From Veterans Administration Hospital, Boise, Idaho, M.I.L. File No. 1539.

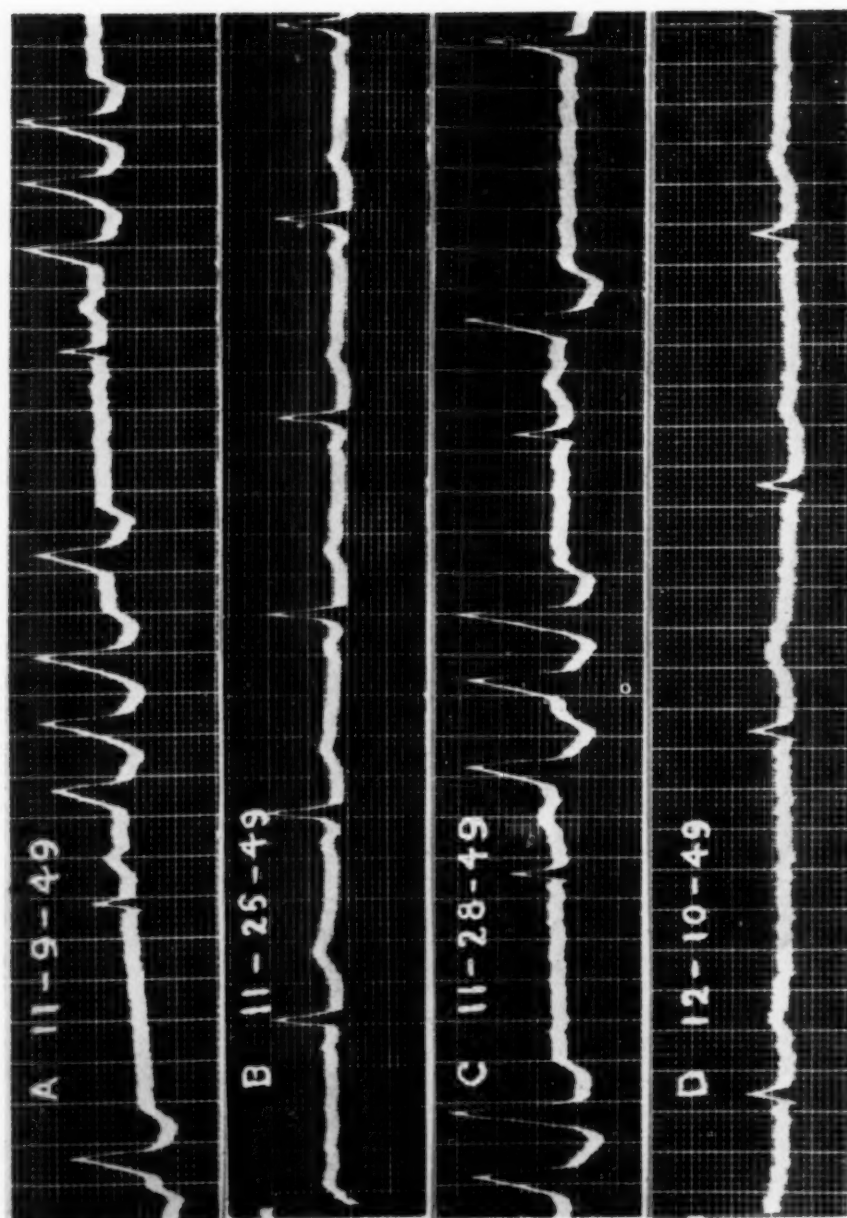


Fig. 3.—Discussed in text. From Veterans Administration Hospital, Boise, Idaho, M.I.L. File No. 1539.

Fig. 2, A is the control tracing showing auricular fibrillation. Fig. 2, B was recorded while the surgeon was digitally exploring the pericardial sac. This shows a regular ventricular rate of 188 with QRS duration 0.14 second and was immediately interpreted as ventricular tachycardia. The epicardium was bathed with several cubic centimeters of one per cent procaine and several minutes later another tracing was recorded as illustrated in Fig. 2, C. Although the more normal appearing complexes are abnormally broad (0.12 second), the complexes displaying aberrant ventricular conduction are bizarre in form, and the QRS duration varies from 0.14 second to 0.18 second. Furthermore, the aberrant ventricular complexes arise when a long cycle (0.50 second or longer) is followed by a short cycle (0.28 second or shorter). The runs of aberrant complexes are terminated by a cycle of relatively long duration.

After the recording of the tracing shown in Fig. 2, C, it was realized that the paroxysm of abnormally broad ventricular complexes shown in Fig. 2, B was probably a paroxysm of supraventricular tachycardia with aberrant ventricular conduction. Following the operation, the patient displayed his usual rhythm of auricular fibrillation without evidence of aberrancy.

Surgical exploration did not reveal any evidence of constrictive pericarditis. The patient made an uneventful recovery but has remained in a state of chronic congestive heart failure of undetermined etiology.

Comment.—This patient with pre-existing auricular fibrillation, exhibited a rapid regular supraventricular tachycardia with aberrant ventricular conduction during surgical manipulation of the heart. Topical application of procaine to the epicardium was followed by reversion to the slower irregular rhythm, now interrupted by short runs of aberrant conduction. The paroxysm of rapid regular rhythm with bizarre complexes was originally mistaken for a ventricular tachycardia, arousing unnecessary concern during operation but was correctly identified on the basis of the subsequent observations.

CASE 3.—A 59-year-old white rancher was admitted to the Fort Logan Veterans Administration Hospital on Nov. 8, 1949, complaining of swelling of the right leg of twenty-four hours duration. For fifteen years previously he had had recurrent attacks of stabbing pain on the left side of the chest associated with shortness of breath which was brought on by exertion and relieved by rest. In March, 1949, he was hospitalized at another hospital for a "heart attack" and he first noted irregularity of his heart at that time. Physical examination revealed a slender elderly chronically ill man weighing 155 pounds. Blood pressure was approximately 140/82 mm. Hg. The heart was enlarged to the left. The apical cardiac rate was 126 per minute and the peripheral rate 84 per minute. The sounds were of good quality with an irregular irregularity. There were a few râles in the lung bases. There was moderate right pretibial edema with tenderness of the right calf and a positive Homans' sign. A diagnosis of phlebothrombosis of the deep veins of the right calf and arteriosclerotic heart disease with congestive heart failure was made. Anticoagulant therapy with Dicumarol was started.

The following day (Nov. 9, 1949) an electrocardiogram was obtained (Fig. 3, A). This revealed auricular fibrillation with runs of broad bizarre ventricular complexes interrupted by occasional normal ventricular complexes. The first normal complex (QRS 0.08 second) in this tracing is followed in 0.5 second by a run of four bizarre ventricular complexes (Rate 181, QRS duration 0.16 second). The last ventricular complex of this "run" is followed by a ventricular pause of 1.0 second when another normal complex is observed. This single complex is followed in 0.48 second by another run of abnormal ventricular complexes. The patient was given a total of 2 Gm. of digitalis, whole leaf, in seven days and noted considerable improvement in his breathing and was less conscious of palpitation. However, a repeat electrocardiogram revealed similar findings.

A diagnosis of runs of ventricular tachycardia was suggested, digitalis was discontinued and quinidine in a dose of 0.2 Gm. three times daily was started on Nov. 18 and increased to 0.4 Gm. on Nov. 21 after which the electrocardiogram revealed a normal sinus rhythm (Nov. 25, Fig. 3, B). However, on Nov. 28, auricular fibrillation was again present with bizarre ventricular complexes

(Fig. 3, C) which is similar to Fig. 3, A except that the last ventricular complex of Fig. 3, C is abnormally broad, even though the postsystolic pause of the preceding complex is 1.4 seconds. Quinidine was increased to 0.4 Gm. four times daily with reversion to a normal sinus rhythm for a short time when auricular fibrillation again intervened. The patient was then again digitalized and in addition maintained on quinidine 0.2 Gm. four times daily. He was discharged as improved on Dec. 10, 1949, (Fig. 3, D).

Comment.—This patient represents a typical case of auricular fibrillation with aberrant ventricular conduction which at first was construed as ventricular tachycardia. Quinidine therapy, though not harmful, was certainly ineffective in the dosage given and it was not until adequate digitalization was carried out that treatment was successful. It is to be noted again that the last ventricular complex in Fig. 3, C displays aberrancy even after a long postsystolic pause of 1.4 seconds, whereas the previous normal ventricular complex is registered after a shorter postsystolic pause of 0.89 second. This finding lacks explanation since it would be expected that a pause of such relatively long duration would allow recovery of the affected branch bundle.

DISCUSSION

Katz⁴ states that aberrant ventricular conduction is recognized by finding a ventricular complex of supraventricular origin which occurs prematurely compared with other ventricular beats, and shows a bizarre appearance and a prolonged QRS duration. This is well shown in Case 1 (Fig. 1, A). Gouaux and Ashman¹ state that aberration occurs when a short cycle follows a long one because the refractory period varies with the length of the preceding cycle. For example, if a cycle of average length is followed by a shorter cycle the impulse may be delayed. However, if a cycle of greater length is followed by a short cycle, then the impulse is blocked in its passage along one of the branch bundles and must traverse the interventricular septum (with its usual delay) before reaching the opposite branch bundle giving a recorded impulse simulating bundle branch block. This is stated to be of the right bundle branch type in 85 per cent of the cases.¹ These authors also state that the impulse is conducted in a retrograde manner by the previously blocked branch bundle upward to the main bundle which is refractory at this time. If another supraventricular impulse is transmitted it again reaches the previously blocked bundle while it is in a refractory state, and the process is repeated until a subsequent impulse arrives at a time late enough to allow sufficient rest of the previously refractory bundle. Rapid auricular discharge such as auricular tachycardia, flutter, or fibrillation with aberrant ventricular conduction often results in a run of such complexes which on superficial analysis may simulate ventricular tachycardia. This is well illustrated in the accompanying figures.

It is obvious then that the usual criteria for differentiation of supraventricular from ventricular tachycardia are not infallible, and an added pitfall may be auricular flutter or fibrillation with aberrant ventricular conduction. As indicated above this may be suspected by finding a cycle of relatively long duration,

followed by a cycle of short duration, and with the aberrant complexes being terminated by a cycle of relatively long duration which allows recovery of the recalcitrant branch bundle.

SUMMARY

1. Three cases are presented with aberrant ventricular conduction which simulated ventricular tachycardia. Two of these cases did not respond to moderate doses of quinidine and treatment was ineffective until adequate digitalization was carried out. One of these had a basic rhythm of normal sinus rhythm, and in the other two patients the basic rhythm was auricular fibrillation. One case with a basic rhythm of auricular fibrillation exhibited supraventricular tachycardia with aberrant ventricular conduction during surgical manipulation of the heart.

2. Prompt recognition of this arrhythmia is desirable since on superficial analysis it simulates paroxysmal ventricular tachycardia. Digitalis is usually contraindicated in the management of paroxysmal ventricular tachycardia but appears to be the drug of choice in paroxysmal supraventricular tachycardia displaying aberrant ventricular conduction.

3. The mechanism of production and the recognition of aberrant ventricular conduction is discussed.

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TRANSIENT VENTRICULAR FIBRILLATION. V.

THE EFFECTS OF THE ORAL ADMINISTRATION OF QUINIDINE SULPHATE ON PATIENTS WITH TRANSIENT VENTRICULAR FIBRILLATION DURING ESTABLISHED ATRIOVENTRICULAR DISSOCIATION.

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THE PURPOSE of this study was to determine the effects of the oral administration of quinidine sulphate on patients with transient ventricular fibrillation during established atrioventricular dissociation. Quinidine sulphate has been found useful in preventing and abolishing transient ventricular fibrillation in a few patients who, between attacks of Adams-Stokes seizures, revealed a normal rhythm.^{1,2} However, evidence that the oral use of this drug may be beneficial in patients with transient ventricular fibrillation during established atrioventricular dissociation is meager,³⁻⁵ and the opinions expressed on its value and limitations under such circumstances are confusing. For example, only recently it has been suggested that, "in spite of current prejudices against the use of quinidine in the presence of conduction defects, when there is graphic evidence that the symptoms of complete heart block are due to episodes of ventricular tachycardia or ventricular fibrillation, it seems reasonable that the use of this drug might be more effective than other drugs that are known to increase ventricular irritability."⁶

Again, Levine and Harvey⁷ state, "that there is reason to believe that the constant oral dose of quinidine may be helpful in decreasing the frequency of syncopal attacks in such patients with established atrioventricular dissociation." Because quinidine has been known to suppress premature beats of the ventricles when normal rhythm was present, Katz⁸ concluded that, "atrioventricular block is a relative contraindication to the use of quinidine unless frequent premature beats are also present." Finally, in the latest expression on the uses of quinidine in disorders of the heart, Gold⁹ states that some cases of Adams-Stokes seizures in which these periods are due to fleeting ventricular fibrillation may be brought under control by quinidine; although in the only patient he had seen with this syndrome, quinidine in the doses used seemed to be of no benefit at all.

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METHOD OF STUDY

Three patients who were subject to recurrent attacks of transient ventricular fibrillation form the basis of this study. One patient, a man, has been under observation at the Montefiore Hospital, New York, N. Y., for over ten years and has been found to respond favorably to the intramuscular injections of atropine sulphate, 1/30 grain, and to the intravenous administration of graded doses of magnesium sulphate.¹⁰ Another patient, a woman, was at the hospital for four and one-half years before she succumbed to a terminal seizure of ventricular fibrillation, and the third patient, a man, has been under study for only one month since he began to experience these attacks.

The natural course of the development of recurrent periods of transient ventricular fibrillation and the alterations in the rhythm of the heart leading to these attacks, as well as the changes that followed the revival of the heart from transient ventricular fibrillation, were studied prior to the experiments.

The patients were kept in the electrocardiographic circuit or under personal supervision throughout the entire day of the experiments so as to be certain of the cardiac mechanisms present at any one time. Continuous electrocardiograms were obtained prior, during, and subsequent to the administration of quinidine and whenever it was found of interest after that. Records were obtained with the patient in the circuit in Lead II only.

No other drugs were used for one week prior to the experiments except atropine sulphate in one patient as indicated in his protocol. The quinidine was given in tablet form in the doses indicated either at hourly intervals or in one larger dose at one time.

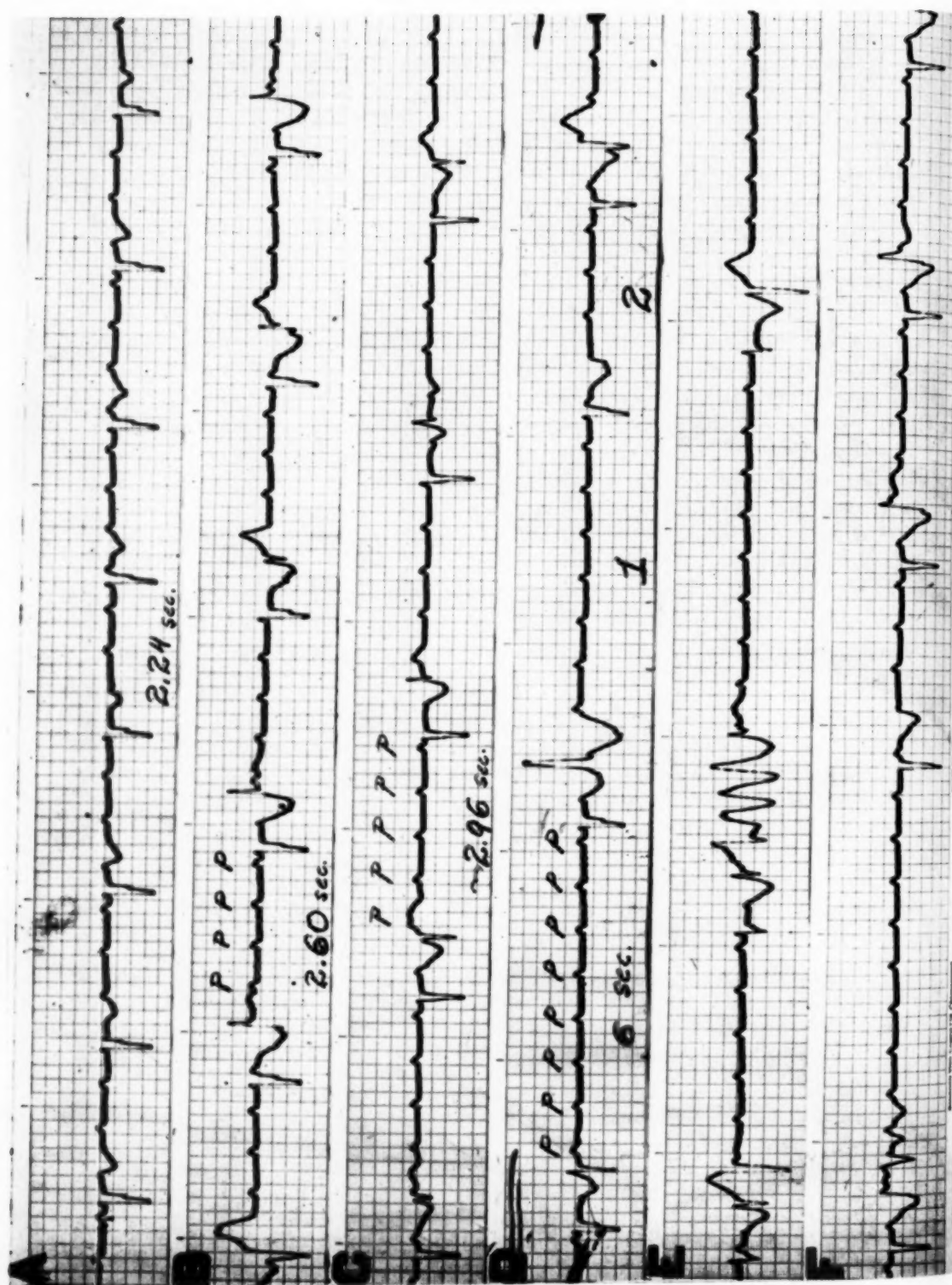
RESULTS

The alterations in the rhythm of the heart induced by the administration of the drug may be best exemplified by a description of the following experiments each one of which depicts a particular action of the drug on the rhythm of the heart. In the light of previous experiences, particular attention was paid to the duration of the pauses which followed the premature beats of the ventricles and on the postfibrillary standstills of the heart that appeared after revival from transient ventricular fibrillation.

The Effects of the Oral Administration of Quinidine Sulphate When Given at Hourly Intervals.—After a control period of four hours, quinidine sulphate was given in 3 grain doses, 0.2 Gm., at hourly intervals to Case 1 at a time when he was free from symptoms and showed a basic ventricular rhythm of 26.8 beats per minute. The atrial rate averaged 100 beats. The duration of each ventricular cycle was 2.24 seconds (Fig. 1, A). No changes in rhythm were noted for the next hour until he received a second dose of 3 grains, 0.2 Gm., of the drug.

Fifteen minutes later, he began to show alternate premature beats of the ventricles. Portions of these premature beats arose from the ascending limbs of the T waves which now had become markedly negative so as to form "deformed ventricular complexes." Such abnormal ventricular complexes have been described in association with spontaneously developing prefibrillary mechanism during established atrioventricular dissociation.¹¹

The returning ventricular cycles following the premature beats measured 2.60 seconds. There were four atrial complexes to each returning ventricular cycle (Fig. 1, B).



Twenty-one minutes after the second dose of quinidine sulphate, the alternate premature beats of the ventricles persisted but now the duration of the returning cycles following the premature beats measured 2.96 seconds and the atrial rate slowed from 100 beats to 93.7 beats per minute (Fig. 1, C). Now there were five atrial beats to each ventricular cycle.

Eight minutes later, the patient began to complain of uneasiness in his chest. Examination of his pulse revealed long pauses with a ventricular rate that averaged only 10 beats per minute not counting the premature beats that were present. Most of these could not be palpated at the wrist but they could be heard at the apical region of the heart.

Electrocardiograms obtained at this time showed that the heart pauses were caused by a further increase in the duration of the returning cycles following the premature beats of the ventricles which now measured 6.00 seconds with 8 atrial complexes to each ventricular beat (Fig. 1, D1). The rate of the atria was 93.7 beats per minute. Such periods of asystole alternated with shorter returning cycles of 3.08 seconds duration (Fig. 1, D2).

One hour and thirty-five minutes after the beginning of the experiment, in addition to these periods of asystole following the premature beats of the ventricles, there appeared a prefibrillary mechanism consisting of short runs of fractionated extra systoles of the ventricles (Fig. 1, E). The combined presence of this mechanism and the ventricular asystole following the post extra systolic period averaged 9 seconds. There was an average of only 6 ventricular contractions per minute at this time so that the patient experienced mild syncopal seizures of brief duration and these persisted on and off for the next four and one-half hours before the effects of the drug wore off.

The same type of alterations in the cardiac mechanism following the use of 3 grains, 0.2 Gm., of quinidine sulphate orally was noted in all three patients with transient ventricular fibrillation during established atrioventricular dissociation, after the use of 2 hourly doses in two patients and 4 hourly doses in the third.

The Effects of the Oral Administration of a Single Dose of 6 Grains of Quinidine Sulphate.—

A second experiment was carried out on the same patient one month later. At this time his cardiac mechanism was in a relatively labile state as a result of extrinsic nerve influences as may be judged by the constant variability of the ventricular cycles from beat to beat. The ventricular complexes were all downwardly directed and the T waves were all negative. The duration of the ventricular cycles varied spontaneously from a minimum of 1.60 second to a maximum of 2.86 seconds (Fig. 2, A 1,2,3). The atrial rate averaged 93.4 beats per minute. After thirty-three minutes of this type of cardiac mechanism during which premature beats of the ventricles were totally absent, the patient was given an oral dose of 6 grains, 0.4 Gm., of quinidine sulphate.

Seventeen minutes later, there appeared a bigeminal rhythm with deformed ventricular complexes in which increasingly negative large T waves were interrupted on their ascending limbs by portions of ventricular premature beats. The returning cycles following the premature beats of the ventricles measured 2.80 seconds (Fig. 2, B1) but these increased abruptly to 3.20 seconds (Fig. 2, B2) so as to alter the rhythm of the heart before there developed a prefibrillary mechanism that consisted of multiple premature beats of the ventricles in rapid succession (Fig. 2, B3).

Within two minutes, runs of ventricular fibrillation set in alternating with a prefibrillary mechanism (Fig. 2, C and D). After lasting three and one-half hours, these alterations in the cardiac mechanism were replaced by alternate premature beats that disappeared on the next day.

Similar changes were noted in this patient during a subsequent experiment in which atropine sulphate, 1/30 grain intramuscularly, had been used to regularize his cardiac mechanism and to test the influence of quinidine sulphate on the extrinsic nerves of the heart.

Six grains of quinidine sulphate, when administered in one dose to the two other patients with transient ventricular fibrillation during established atrioventricular dissociation, resulted in the development of identical alterations in the rhythm of the heart except for the time of their appearance, which varied from one hour to three and one-half hours, respectively.

Fig. 1.—A, Control record showing atrioventricular dissociation with an average ventricular cycle of 2.24 seconds. B, Fifteen minutes after a second dose of 3 grains of quinidine. Premature beats of the ventricles with an increase in duration of ventricular cycles to 2.60 seconds. C, D, E, and F, progressive increase in duration of returning ventricular cycles with short runs of prefibrillary periods.

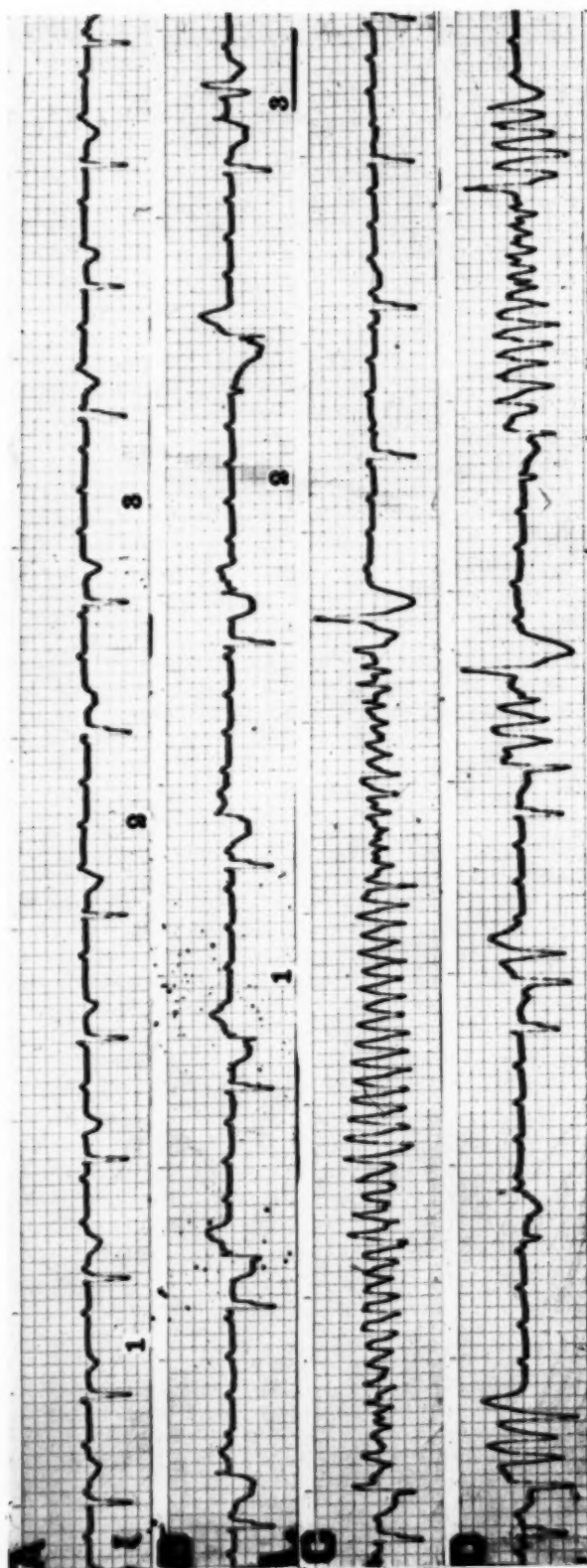


Fig. 2.—A, Control record showing variability in duration of ventricular cycles from 1.60 to 2.86 seconds. B, Seventeen minutes after the use of a single dose of 6 grains of quinidine sulphate. Premature beats of the ventricles with abrupt increases in duration of returning ventricular cycles (1:2). C,D, Two minutes later. A period of transient ventricular fibrillation followed by recurrent fibrillary periods.

The Effects of the Oral Administration of a Single Dose of 10 Grains of Quinidine Sulfate.—After a control period lasting a whole morning, 10 grains of quinidine, 0.67 Gm., were administered at one time to a patient when he was free from symptoms and when his basic ventricular rate averaged 24 beats per minute in the absence of any premature beats of the ventricles. Within nine and one-half minutes there developed a prefibrillary period lasting 30 seconds followed by the abrupt onset of a transient seizure of ventricular fibrillation of 1 minute and 43 seconds duration (Fig. 3, A).

At this time the patient lost consciousness. A period of rapid breathing was followed by total apnea and pallor was replaced by intense cyanosis. Convulsive movements appeared after 30 seconds during which no heart sounds were audible and no pulses were palpable. A sudden flush of the skin associated with a shrill cry and incoherent speech heralded the termination of the fibrillary process and the revival of the heart from this attack.

Fibrillation was ended by a short postundulatory pause measuring 0.4 second (Fig. 3, A1). The first effective ventricular contraction occurred 3.60 seconds after the last of the fibrillary waves (Fig. 3, A2). The succeeding ventricular cycles measured as follows: 1.32 second, 1.28 second, 1.40 second, 3.76 seconds, and 3.48 seconds. There then followed a short series of ventricular cycles averaging 3.52 seconds before the onset of the so-called first postfibrillary tachysystole. This consisted of an irregular acceleration of the ventricles averaging 140 beats per minute with the atria trying to keep pace (Fig. 3, B).

A second period of ventricular slowing ended this heart hurry which lasted 78 seconds (Fig. 3, C1). There then followed a second period of ventricular acceleration with the ventricles beating at 38.4 beats per minute (Fig. 3, D) and this lasted 14 minutes and 8 seconds. After that, the rhythm consisted of atrioventricular dissociation interrupted by premature beats of the ventricles with shorter runs of ventricular fibrillation that disappeared entirely twelve hours after the use of quinidine.

Of particular interest are the effects which the same dose of the drug had on the postfibrillary period following the revival of the heart from an attack of ventricular fibrillation in another patient. Preliminary alterations in the rhythm of the heart began to appear 17 minutes after the use of quinidine. Following recurrent short prefibrillary periods that lasted one hour and 20 minutes, there set in abruptly a seizure of transient ventricular fibrillation of 27 seconds duration. A postundulatory pause with 8 atrial beats was followed by an effective ventricular contraction (Fig. 4, A S₁). The duration of the succeeding ventricular cycles in this postfibrillary period varied markedly from moment to moment (Table I). There was a shifting of the idioventricular pacemaker of the heart for a few beats but for the next few minutes periods of asystole lasting 22.56 seconds and 25.4 seconds respectively alternated with periods of slowing of the ventricles of shorter duration of from 3.4 to 7.44 seconds (Fig. 4, A and B).

In the meantime, the atrial rate which averaged 75 beats per minute before the experiments now slowed temporarily to 42.3 beats per minute.

During this interval of recurrent ventricular cessation which lasted about 10 minutes, the patient was unconscious. He was intensely cyanotic and perspired profusely. His respirations were irregular and at times short runs of rapid breathing ended in apnea only to be interrupted by the Cheyne-Stokes type of breathing. Such respiratory variations persisted for several hours and were interrupted by repeated convulsive movements. It was difficult to determine whether these were the result of the toxic action of the drug on the central nervous system or the result of alterations in the rhythm of the heart.

The return of the original basic ventricular rate and rhythm from this episode was through a slight acceleration of the idioventricular rhythm of 33 beats per minute, (Fig. 4, D), and then 40.2 beats per minute (Fig. 4, E). This waxing and waning of the heart rate lasted for the ensuing two hours before the return of the original rate of 24 beats per minute. However, the ventricular complexes were accompanied now by very large negative T waves indicating marked depression of conduction within the ventricles (Fig. 4, G). The atria which had accelerated with the ventricles slowed from 100 beats per minute to 71.3 beats and remained so for nine hours after the beginning of the experiment.

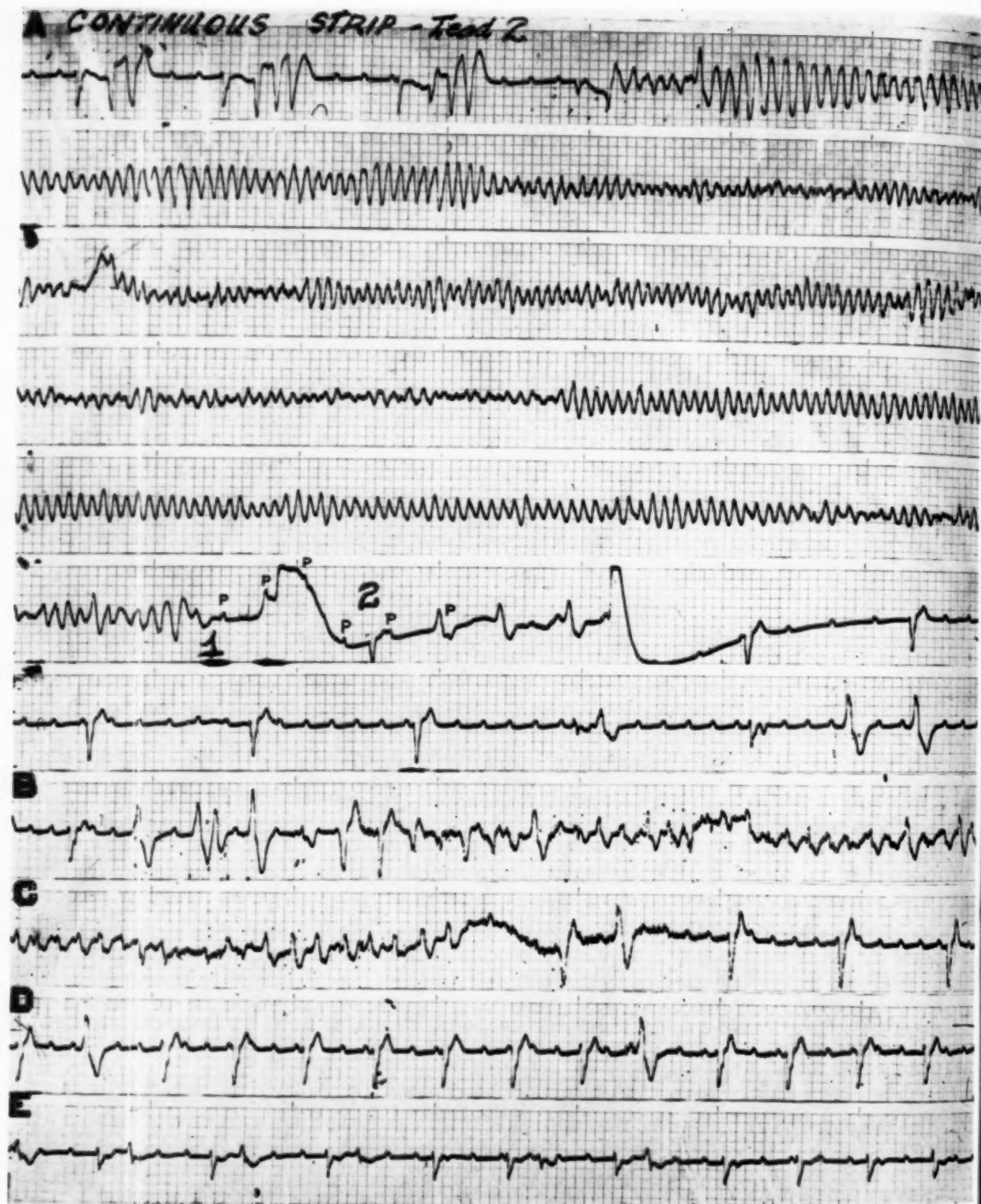


Fig. 3.—A, A period of transient ventricular fibrillation appearing nine and one-half minutes after a single dose of 10 grains of quinidine sulphate. B,C,D,E, mode of recovery from transient ventricular fibrillation is through the appearance of alternate periods of slowing and acceleration of the ventricles.

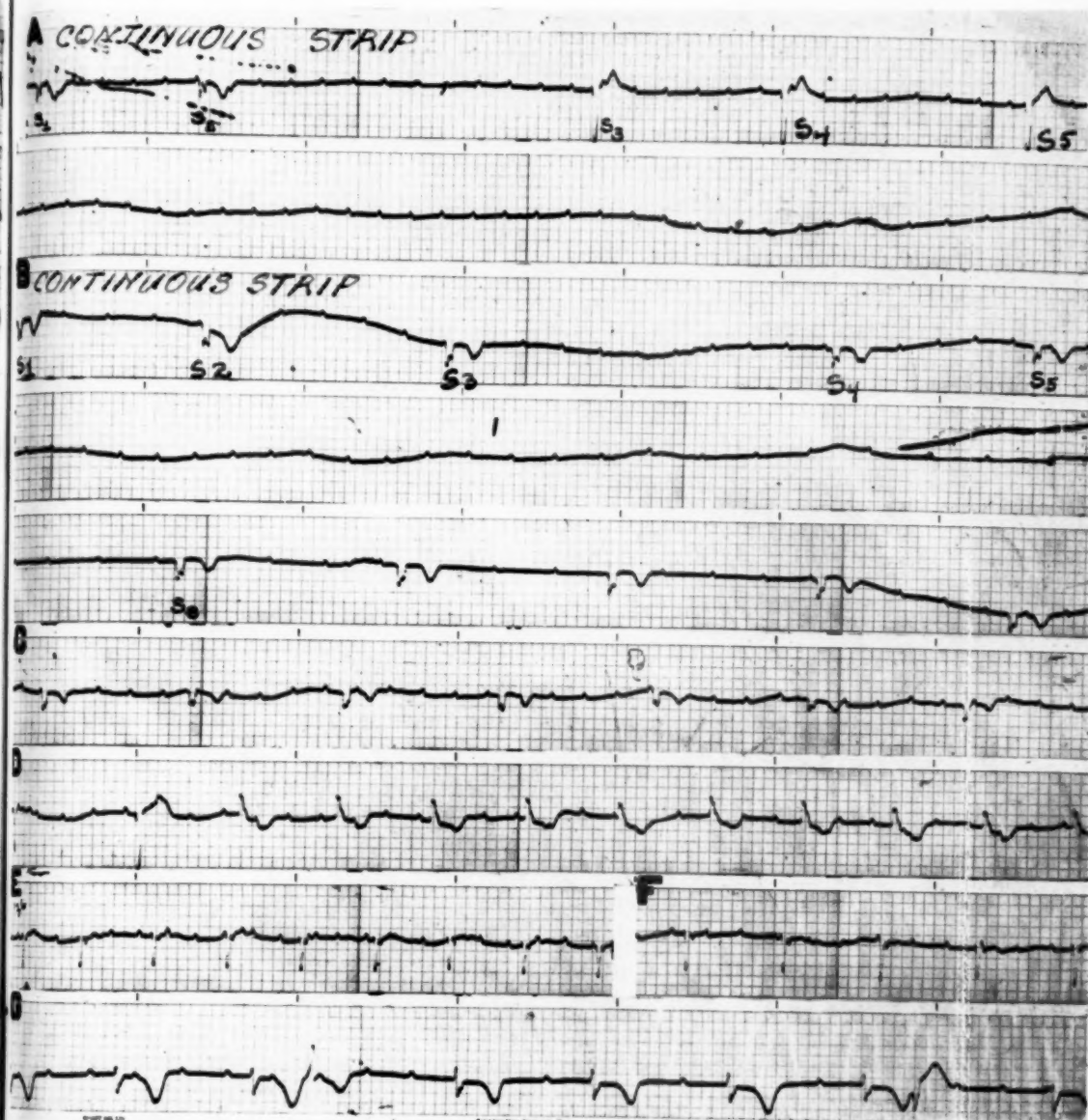


Fig. 4.—Mode of recovery from a period of transient ventricular fibrillation that appeared one hour and twenty minutes after the use of quinidine sulphate. Note recurrent periods of complete ventricular asystole A,B before return to a basic rhythm through progressive increase of idioventricular rhythm, (C,D,E,F,G.)

DISCUSSION

Contrary to general belief, these observations reveal that when quinidine sulphate is administered orally in graded doses to patients with transient ventricular fibrillation, during established atrioventricular dissociation, there appear

TABLE I. THE EFFECTS OF QUINIDINE SULPHATE ON THE DURATION OF VENTRICULAR CYCLES IMMEDIATELY AFTER CESSATION OF TRANSIENT VENTRICULAR FIBRILLATION—THE SO-CALLED POSTFIBRILLARY STANDSTILL PERIOD OF THE VENTRICLES. CONTROL NORMAL CYCLE = 2.24 SECONDS

TIME AFTER QUINIDINE (0.6 Gm.)	NUMBER OF VENTRICULAR CYCLES	DURATION OF VENTRICULAR CYCLES IN SECONDS
1 hr. 26 min.	1	3.34
	2	7.44
	3	3.48
	4	4.64
	5	22.56
1 hr. 30 min.	1	3.88
	2	4.48
	3	5.32
	4	3.80
	5	25.4
	6	4.16
1 hr. 51 min.	Average	2.28
1 hr. 63 min.	Average	1.80
2 hr. 15 min.	Average	1.80

alterations in the rhythm of the heart that lead to the onset of such periods of ventricular fibrillation instead of their abolition.

The development, duration, severity, and disappearance of these abnormal cardiac mechanisms depend in part upon the dosage of the drug, the larger dose given at any one time yielding the graver symptoms and signs. However, attention is called to the fact that there is a great variability in the onset and offset of abnormal rhythms following the same dose in the same patient and in different patients. The action of quinidine was found to be directly on the heart muscle since its effects were noted in atropinized patients as well as when the underlying cardiac mechanism was very labile because of extrinsic nervous influences.

In contrast to the earliest effects on such patients by procaine amide¹² which depresses the rhythmicity of the atrioventricular pacemaker, the first effects of quinidine sulphate were noted on intraventricular conduction of the ventricles. This was reflected in the early appearance of progressive enlargement and negativity of the T waves with prolongation of the associated RS-T segments. Added to this, the simultaneous development of premature beats arising from the ascending limbs of these T waves yielded deformed ventricular complexes that have always been found to be the forerunners of transient periods of ventricular fibrillation.

A second change resulting from quinidine was the progressive increase in the duration of the returning cycles which followed premature beats of the ventricles that appeared at the same time. When complete heart block is present and the ventricular rhythm is disturbed by a ventricular extra systole, the length of the returning cycle is precisely that of the initial cycle.¹³ Sometimes the returning cycle is shorter than the initial cycle. The returning cycle has been found to increase in duration after repeated attacks of transient ventricular fibrillation when the heart was fatigued by rapid beating. However, such drugs as procaine amide and quinidine sulphate effect this change very early after their use. At

times, only the cycle after a single extra systole is prolonged, but more often the cycles following multiple premature beats in rapid succession show the changes. Obviously, these alterations in the rhythm of the heart occurring at such times are the result of an increase in the refractoriness of the heart muscle to stimuli and yield a depression in both rhythmicity and irritability at the same time.

Again, repeated records on the mode of revival of the heart from transient periods of ventricular fibrillation during established atrioventricular dissociation have shown several types of alterations in the rhythm of the heart after the end of fibrillatory process. The shorter runs were terminated by single premature beats of the ventricles or by groups of these in rapid succession followed by a postundulatory pause.¹⁴ The basic rhythm which was present before the onset of ventricular fibrillation returned immediately. However, if the attacks of ventricular fibrillation were frequent and lasting there then developed a prolonged period of ventricular asystole succeeded by periodic standstill of the ventricles and atria when the fibrillatory process ended.¹⁵

It was pointed out by Cushny¹⁶ that when the atria and ventricles were separated in the experimental animal and the usual slow rhythm of the ventricles was accelerated at such times by a series of shocks at a more rapid rate, the ventricles did not resume their original rhythm when the stimulus was withdrawn. They remained quiescent for a time and then recommenced beating very slowly and irregularly accelerating their rhythm until there was a return to the original rate before stimulation.

The factors responsible for the appearance of these pauses were attributed in part to the duration of the stimulus applied and in part to fatigue with its attendant anoxemia increasing for some time after acceleration had ceased.

This type of retarded rhythmicity and irritability has its counterpart in the alterations in the rhythm of the heart that may appear after transient ventricular fibrillation has ceased.

Quinidine causes such changes to appear earlier than usually. The drug causes a prolongation of ventricular standstill immediately after fibrillation ceases. It is responsible for such marked depression of the rhythmic center in the atrioventricular node that periodic asystole of the ventricles recurs with increasing frequency and duration after its use. Furthermore, the drug depresses irritability in the lower centers of the ventricles by preventing the development of the postfibrillatory periods of tachysystole that usually follow ventricular standstill in the revival of the heart from transient ventricular fibrillation. Because of these profound disturbances, it is distinctly contraindicated in such patients.

CONCLUSIONS

A study was made of the effects of the oral administration of quinidine sulphate on three patients with transient fibrillation during established atrioventricular dissociation.

The drug was administered in graded doses and it was determined that in the same doses its action was variable from patient to patient. The duration of its effects as judged by the alterations in the cardiac rhythms and the intensity of its action depended upon the size of the dose.

Quinidine sulphate depressed conduction within the ventricles very early after its use as indicated (a) by an unusual prolongation of the RS-T or Q-T segments; (b) by the appearance of progressively increasing negative T waves; and (c) by the development of deformed ventricular complexes associated with the onset of premature beats of the ventricles, only portions of which were superimposed on the ascending limbs of the T waves. These changes which appeared early after the use of the drug were similar to the changes observed as preliminary events in the natural course of transient ventricular fibrillation.

Quinidine sulphate increased the refractory period of the ventricles as may be judged by the early unusual prolongation of the returning cycles following the premature beats of the ventricles when they appeared during established atrioventricular dissociation.

The drug was responsible for the development of recurrent periods of transient ventricular fibrillation that persisted for hours once the mechanism set in following its use.

Quinidine sulphate was found to depress both rhythmicity and irritability of the heart by its profound effects on the alterations in the rhythm of the heart following immediately after cessation of transient ventricular fibrillation. Long pauses of asystole of the ventricles ended the fibrillary process and the impulse-building centers in the atrioventricular node and ventricles were retarded. The drug augmented the effects of fatigue and rapid stimulation of the heart in the postfibrillatory period.

Unlike procaine amide, quinidine did not influence the rhythmic center in the atrioventricular node unless conduction disturbances and refractoriness were affected first. The duration of the action of quinidine on such patients was longer than that of procaine even when smaller doses were used.

Quinidine sulphate is contraindicated in patients with transient ventricular fibrillation during established atrioventricular dissociation.

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ELECTROCARDIOGRAPHIC MIRROR PATTERN STUDIES. I.

EXPERIMENTAL VALIDITY TESTS OF THE DIPOLE HYPOTHESIS AND OF THE CENTRAL TERMINAL THEORY

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ALTHOUGH Einthoven's limb leads have been generally accepted in routine electrocardiographic procedure, adoption of these leads does not necessarily imply full acceptance of all the vector and dipole concepts implicit in Einthoven theory. It is indeed possible to make valid differentiations between normal subjects and cardiac patients for given lead combinations essentially without reference to any particular theory.

The Einthoven assumptions of an equivalent conductive sphere with vector dipole source and three symmetrically placed leads were the object of an extensive and still continuing controversy, but most electrocardiographers now seem to support the view that the deviations resulting from these assumptions are not large enough to invalidate Einthoven's theory. In fact, with the development of vectorelectrocardiography there is a tendency to revert to the dipole-theory¹⁻⁴ even in its simplest terms.⁵

It is obvious, however, that in any attempt to establish theories which describe the electrical behavior of the heart in terms of simple equivalent models, we are bound to run into quantitative inconsistencies and qualitative contradictions. Extended arguments will never prove one such theory right and another wrong, for all of these theories offer at best fair approximations and are not intended to be quantitatively accurate as are some of the physical laws. The questions which we may properly ask are: (1) how far can a simple theory be pushed before it yields results which are incorrect by more than a specified error, and (2) how much complication in increased complexity of measurement and involvement of theory is required to improve the accuracy of results significantly?

Development of objective tests that would discriminate between those theoretical concepts which are still sufficiently valid as bases for electrocardiographic interpretation, and those which are so badly distorted as to be valueless or even misleading might help to decide these questions experimentally. We

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have attempted to develop such tests,^{6,7} and in this paper a method will be described which indicates, in a semiquantitative way, how right or wrong our answers are likely to be when based on the assumptions of a dipole heart in the center of a uniformly conductive body, using an improved Wilson type central terminal for reference.

Specifically, we have measured residual potentials in normal and diseased persons from electrode sites connected to form an electrical bridge circuit. The circuit was arranged in such a way that the potentials from two electrode sites referred to a central terminal could be cancelled out exactly if the heart behaved like a true dipole, and if the other usual assumptions were valid.

As the residual potentials should ideally equal zero, their magnitudes should serve as a measure of the errors implicit in the simplified theory. This null technique has the advantage that it emphasizes the shortcomings of theory instead of obscuring them.

THEORETICAL BACKGROUND

There are at least seven important approximations which must be made in any of the theoretical electrocardiographic analyses.

1. We must assume that the heart is so small that it can be treated as a point source of dipole current in a large volume of conductive fluid or alternatively so large that each part of its surface may be regarded as a large flat plane.
2. We must assume some reasonably simple geometric form for the chest. It is usual to choose a sphere for this purpose, but more accuracy without too much additional mathematical complication is obtained by assuming an ellipsoid.
3. It is necessary to assume electrical linearity (but not isotropy) for the chest contents and to select appropriate values of conductivity.
4. It must be assumed that the leads are taken at specified locations on the reference geometrical figure.
5. Unless only bipolar measurements are to be considered, some compromise must be made to derive a so-called indifferent reference potential level (that is, a central terminal, or its equivalent, must be chosen).
6. The spatial shift of the electrical heart center during activity must be neglected.
7. It is also usually assumed that the heart is symmetrically located within the reference volume.

The first of these approximations is perhaps the hardest to accept. The heart is really much too large to be treated as an ideal dipole and is far too small to be treated as an extended uniform source. Conventionally one expects ideal dipole theory to apply within engineering accuracy only for measurements made at least three diameters away from a source. We must thus expect the dipole approximation to be a certain source of error of at least several per cent and perhaps of very much larger errors. These errors will show up as asymmetry potentials and phase errors in measurements made in various anatomic directions. Because of the near symmetry and progressive synchronization of the normal heart cycle, the heart acts much more nearly like a dipole source for nearby measurements than would a distributed current source of equal size composed of randomly arranged dipoles.

Deviations from geometric simplicity must influence the magnitudes and components of potential to be expected at various locations and to exaggerate the errors due to finite heart size. It is next to impossible to predict with any accuracy on purely theoretical grounds where on the surface of the body the potentials representing pure front to back, left to right, and up to down components of ideal dipole current will appear.

Determination of a suitable reference or "indifferent" electrode which is equivalent to an electrode at the electrical heart center proves a very difficult and important job indeed. The error associated with imperfect selection of an indifferent electrode is probably comparable with the error implicit in the assumption of a point heart.

The nonuniform conductivity of the chest contents is also an important factor which influences the recorded electrical patterns. The chest is not equivalent to a corresponding shell full of physiologic saline⁸ but has quite a lot of electrical structure. Its conductivity is indeed relatively low. It is customary also to neglect the electrically reactive characteristics of the chest contents which would cause a differential delay and attenuation of the heart potential components according to their frequency distribution. These factors have not been well worked out but are probably not negligible.

Practically, we would like to think of the heart as a localized source of current changing in magnitude and direction during the beat but remaining substantially in one place. This place, characterized as the heart center, must also be representable by the general type of central terminal obtained by combining the potentials at several external locations in some linear way.

Perhaps the most striking characteristic of an ideal dipole source under these circumstances is its mirror property. Along any line going through the dipole position, not necessarily along the dipole direction, the magnitudes of potential referred to a true central terminal will have a fixed distribution, rising rapidly as the distance from the dipole decreases and changing sign as the dipole is passed then decreasing again in a regular fashion. As the dipole rotates and changes in magnitude to give the usual multiphasic unipolar potential record from a lead placed at any chosen point on the surface of the body, there should be along a line going through the heart and ending at the chosen point a whole family of patterns differing only in size and sign but not in form. This line upon extension to the body surface at an opposite point should yield at this second locus an exact mirror pattern of that at the original point. Because of body shape and inhomogeneity, the internal lines of constant pattern could not be expected actually to be straight. Their form in general would be that of a curve terminating at roughly opposite loci through the heart and passing through the electrical heart center.

As this analysis applies not only to a single current vector but equally well to any combination of vector sources whether constant or varying, we can conclude that at such pairs of opposite positions which we can call *mirror loci* there should always be found identical electrocardiograms of opposite polarity and usually of different magnitude but always representing the current component along the line connecting them through the heart center.

In order to understand the formation of mirror patterns more exactly, let us examine the composition of surface electrocardiographic potentials in terms of a concentrated central current vector of arbitrary and variable direction and magnitude. Let us arbitrarily establish a conventional Cartesian coordinate reference system x, y, z at the heart center where the coordinate directions are, as yet, unspecified. Let us resolve the total current vector into its components in the new reference system so that $X = f_x(t)$, $Y = f_y(t)$, $Z = f_z(t)$. This resolution implies no loss in generality as this set of components is fully equivalent to the initial vector. The functional forms f_x , f_y , f_z are, of course, dependent upon the orientation of the reference frame chosen but are functions only of time once this choice has been made.

Now if reactive components of tissue impedance are negligible, if the tissue conductance is linear with current, and if the concentrated dipole assumption is admissible, it is possible to write the potential V_R^* at any chosen reference point R on the body surface referred to an ideal central terminal in the form $V_R = \alpha X + \beta Y + \gamma Z$ where α , β , and γ are constants for any one surface locus and can be thought of as transfer impedance coefficients. α , β , and γ are all different functions of position on the body surface and are dependent upon the choice of the x, y, z coordinate system, but for any set of these choices are pure algebraic coefficients and are not time dependent.

For a second or "search" locus S on the body there will be a corresponding new set of coefficients α' , β' , γ' expressing the geometry for this new position but, it should be noted, the functional relations f_x , f_y , f_z are still the original ones.

We are now ready to select the coordinate orientation. Remembering that α , β , and γ represent essentially the scaled "projection" factors for the central vector components for the reference position R , let us rotate the x, y, z system until two of these projections (say the β and γ) vanish. This is always possible for the same reason that a plane can always be found perpendicular to any given line and in this plane the line has zero projection in any direction. This choice of coordinates now reduces the expression for the potential at the reference locus to simply $V_R = \alpha X = \alpha f_x(t)$.

In general, however, this choice of coordinates will not reduce α' , β' , or γ' to zero and consequently the potential at an arbitrary search locus, V_S , will contain significant components due to X , Y , and Z . But now, if the search locus is shifted over the body surface, a line will in general be found along which β' is zero. This must be true at R and will, for body shapes approximating the ellipsoid, approach a band around the body in a plane perpendicular to the y direction.

Similarly a band will normally be found on the surface where γ' changes sign and consequently has a zero value. This band will normally lie roughly in a plane perpendicular to the z direction.

Where the band of zero β' crosses the band of zero γ' , unique points are defined where β' and γ' are both zero. At these points the potential variation

* V_R denotes voltage at a reference locus, and should not be confused with Lead V_R .

with respect to a central terminal will be $V_S = \alpha'X + OY + OZ$. Consequently for these points $V_R = \alpha X$, $V_S = \alpha'X$,

$$\frac{V_R}{V_S} = \frac{\alpha}{\alpha'} X = \frac{\alpha}{\alpha'} f_x(t).$$

This is the mirror condition and can be established for any starting point R and its conjugate S. As the points R and S are oppositely located, α' will ordinarily have an opposite sign from α and so the ratio α/α' will have a negative sign. No restrictions were placed on the initial choice of R so any number of pairs of conjugate points should be locatable but since each pair would require a different choice of axes, the α/α' ratios found need not be the same. Indeed the α/α' ratios express to a degree the relative "electrical distance" to the heart center for the two points of each pair.

Turning now to the theory of the simple Wheatstone's bridge (Fig. 1,A), it will be seen that the two mirror potentials, αX and $\alpha'X$, with respect to the central terminal may be regarded as the potential differences across two adjacent arms of a bridge circuit of unknown dividing ratio α/α' . An additional pair of resistances R and R' connected between the points would complete the bridge and, if correctly chosen, should provide a common point which will always be equipotential with the central terminal.

By using a single adjustable potentiometer to form the two arms, the dividing ratio can be given any value between zero and infinity, and consequently there must be some setting where perfect cancellations will occur, and this setting can be found experimentally by simple trial and error.

To summarize the argument then for any arbitrarily chosen point on the body there will be, in general, some voltage due to each component of the total vector heart current at every instant during the beat. To the extent that it is fair to use the point dipole concept, it is also fair to insist that components of current due to different heart muscle fibers must be superimposable vectorially and, consequently, representable at any instant by a single resultant vector.

For this composite vector there must always be some direction of reresolution such that two of the three components will disappear exactly, and there will be, in general, a conjugate position where the same two components cancel, leaving a single proportional component at each position when measured against a proper central terminal.

Improper anatomic choice of the conjugate point will, in general, yield residuals of the other two components when bridge balance is sought because slightly different vector resolutions apply to the two points. As these points lie in a surface (the body surface), there are still two degrees of freedom available, and ideally one can expect to find a mirror locus by judicious readjustment of electrode position. In effect, we balance out one component of the central vector with the external bridge potentiometer and the other two by adjustment of search electrode positions in two different directions. We thus have, in effect, a triple balance bridge with nearly independent adjustments for each of the three balance conditions.

The whole mirror cancellation method is thus based on choosing a test procedure which will yield a zero answer only if none of the assumptions implicit in dipole theory or central terminal theory are violated and then using the total residual deviation measured as a test of validity.

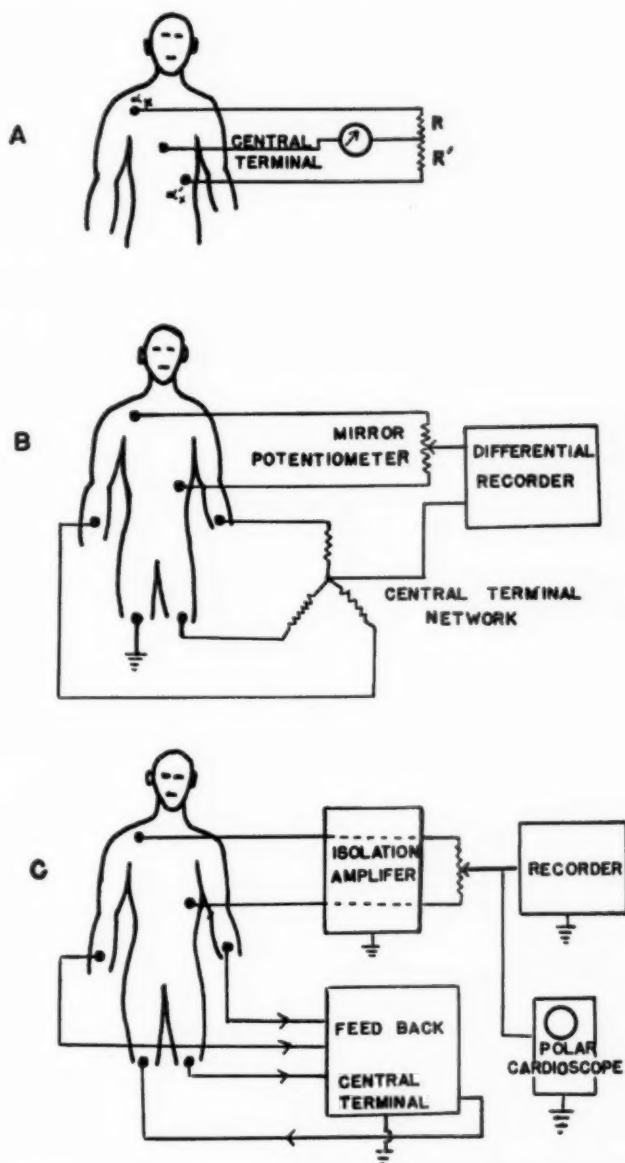


Fig. 1.—Diagrammatic representation of mirror pattern measurement systems: *A*, Idealized bridge circuit equivalent of the mirror pattern measuring system. *B*, Simplified mirror pattern measuring system actually used for some measurements. The potentiometer is of high resistance (100,000 ohms) to reduce current drain and is well shielded. The central terminal network is a conventional one incorporated in a standard recorder (Sanborn). *C*, A more refined measuring system reduces the loading on the electrodes still further, uses a fed-back central terminal to reduce interference and permit choice of central terminal network. The polar cardioscope permits continuous observation of the signal on a fast time base without waste of recording paper.

TECHNICAL PROCEDURES

Instrumentation for the proposed tests of dipole theory validity would appear to be very simple. It would seem necessary only to connect a potentiometer between two loci to be tested and to measure the potential at the movable tap of the potentiometer with a standard electrocardiograph containing within itself the required central terminal network for reference (Fig. 1, *B*).

While this procedure will work and has been used in some of our measurements, it is subject to criticism in several respects and has been replaced by a more ideal system (Fig. 1, *C*). For the potentiometer divider we have used a precision wire wound control directly calibrated in percentage and in arm ratios and have made electronic arrangements for keeping the resistance load seen from the electrodes very high (100,000 ohms or more at all times). This arrangement permits use of relatively small, easily moved probe electrodes with which very little electrode paste is required.

In order to assure immunity from interference and polarization effects and to allow examination of signals in the 100 to 1,000 cycles per second region which are ordinarily suppressed by recorders, two channels of a special six channel amplifier and recording system were used in some of the experiments. This amplifier used a feedback driven central terminal⁹ to minimize 60 cycle interferences and to reduce electrode currents. It has a bandpass extending from 0.1 cycles per second to beyond 5,000 cycles per second. Especial attention has to be given to amplifier noise reduction as most cancellations occur in the 10 to 100 microvolt region and noise is necessarily increased as bandwidth is extended.

While an ordinary hot stylus writer of the Sanborn type is used to record data, our balances are usually made with the aid of a newly developed polar cardioscope using a circularly swept cathode ray tube of the long persistence type. This unit by running continually and showing each heartbeat on a base line nearly ten inches long permits very nice balances to be obtained and displays to good advantage the fast phases of the QRS complex which are normally seen only as a vertical pen stroke. The importance of these fast components will be shown later in reference to "true" and "false" mirror patterns.

In conducting a typical experiment, the patient is seated on a stool so that free access can be had to chest and back. An initial electrode position is chosen and an ordinary small electrode strapped on in the usual fashion; this we call the reference electrode. A second electrode, either hand held or suction type, is now located at a position anatomically opposite through the heart center; this we call the search electrode. An attempt is now made to adjust the bridge balance potentiometer to eliminate all trace of the recorded potential. Often parts of the signal can be cancelled but others cannot. Typically it will be impossible to get optimal balances for the T wave at exactly the same setting as for QRS. Noting the approximate details of the residual and having made a recording with the Sanborn instrument of the residual potential for best balance conditions and of the total potential at both reference and search electrodes, a new search location is chosen an inch or two from the original position. The new position will be better or worse or perhaps about as good as the initial. Usually three or four trials are required to establish the best cancellation location available with fair

accuracy and the residual for this position is then carefully recorded and the final search and reference position marked on the skin with ink or colored pencil. Further search will better the cancellation appreciably but will increase the time required very substantially.

The whole set of measurements is now repeated for additional reference positions until at least three or four mirror loci have been marked for widely varied directions through the heart. This procedure requires at least an hour for completion and consequently cannot be done for very many different loci especially with weak patients.

In order to visualize accurately the spatial configuration of the several electrical axes determined by the sets of mirror points, the apparatus illustrated in Fig. 2 was developed. It comprises a simple steel rod framework fitted with special spring loaded probes. Each probe is made with a large section of prestressed spring so that it is relatively rigid when free but may easily be bent. The probe is held in a universal clamp so that its tip may be adjusted to touch any position on the patient's body when he stands at the center of the steel frame. Threaded through half of the probes there is a chalked white cord terminating in a small but powerful Alnico magnet at the tip and loaded at the back end with a small lead counterweight. On the other probes there is no magnet but only a mild steel tip.

After mirror loci have been determined, the subject stands in the steel frame and one of the probes is adjusted to touch each of the marked reference loci and the corresponding search mirror loci which offered the best cancellation for each reference. A probe with magnet and string is used for each reference location and a steel tipped probe for each search locus.

The subject is photographed from two directions with an ordinary or a stereoscopic camera using electronic flash illumination and is then instructed to push his way out from among the probes. The probes bend but quickly snap back precisely to their original positions and are then connected in pairs by the strings using the magnets for fasteners. Each chalked string now represents one electrical axis, and the whole configuration inside the body of the subject is clearly shown by making a double exposure this time with the strings in place.

Roentgenographically determined edges for the heart are normally sketched in on the subject's chest, and standard cardiographic levels are also marked so that with the double exposure pictures taken from two directions, full face and side, practically complete data are available in permanent form.

While mirror loci can often be determined accurately enough to give significance to electrode position variations as slight as one-half inch, we do not ordinarily attempt to specify the position more accurately than to the nearest unit of level and circumferential position. The actual marked spots are used, however, in making the double exposure photographs. As can be seen in Fig. 2, the axes determined in this way converge within a volume roughly that of the heart.

RESULTS AND DISCUSSION

As a more thorough analysis of the mirror cancellation results will be made in the succeeding papers, we will deal here only with representative sample results.

An effort will be made, however, to emphasize the detailed methods of analysis as the analytic criteria strongly influence the conclusions.

Crucial to the whole discussion of mirror patterns is the choice of residual potential which we shall permit in the categories which we will later term "excellent," "good," "poor," and "bad." In the first place we must remember that

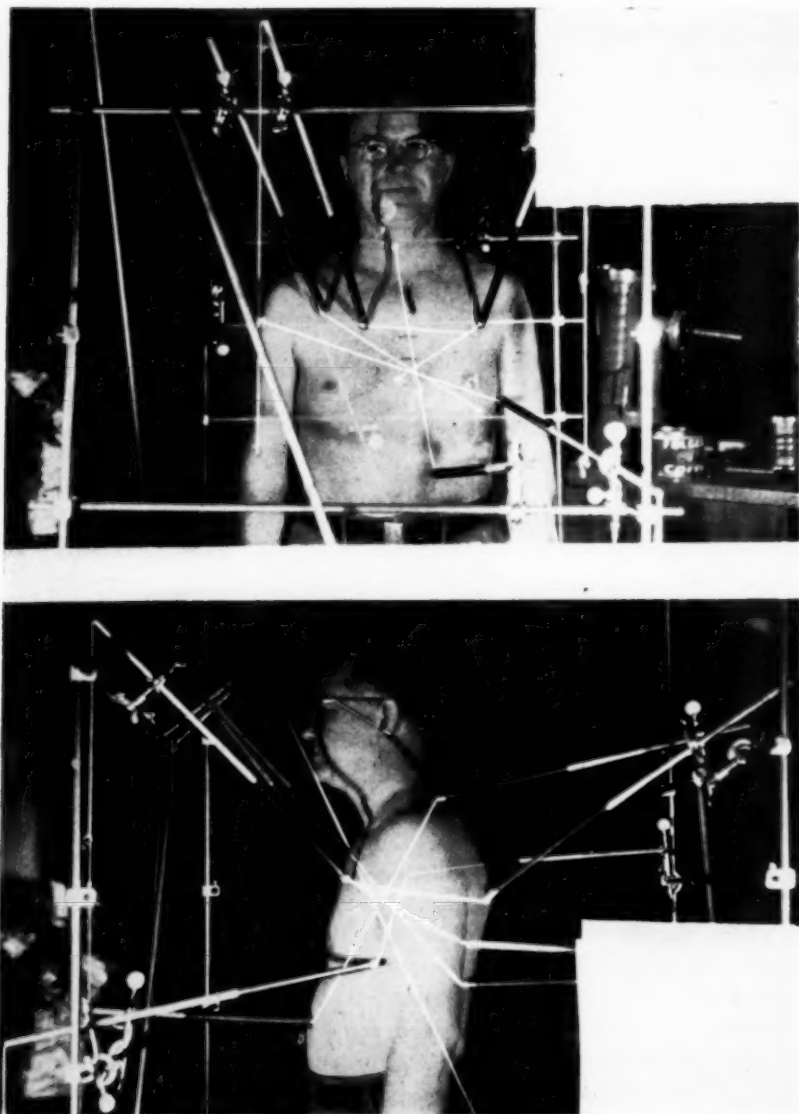


Fig. 2.—Spatial intersection of electrical mirror axes: Adjustable probes are placed against the subject's body at positions corresponding to loci at which search and reference patterns have been located. The subject is photographed from two directions and then pushes out from between spring probes. Probes return to original position and are connected by white strings which are photographed by double exposure to reveal mirror axes. Subject has posterior infarct. Note that axes intersect in limited region in both planes.

the magnitude of the whole electrocardiogram at any point on the body surface as referred to the central terminal may vary greatly according to location. On the chest just over the heart it is not unusual to find potentials of several millivolts while on the back it is normal to find only a fraction of a millivolt.

If we consider a cancellation with residual below some arbitrary size, say 0.05 millivolt, as excellent, we will seldom get excellent cancellation for locations yielding large individual potentials even though the residual is small relatively. We must therefore take into consideration the size of the contributing potentials.

Against this policy, however, is the theoretical fact that an improperly chosen central terminal contributes a constant voltage residual irrespective of search and reference locations chosen. This error may at times be a compensatory one but it is present nonetheless.

According to one scheme which we considered, the residual would be compared with the average of the maxima for the two components obtained individually at the reference and search locations. This criterion gives excessively good results, however, when one of the potentials is very large and the other very small even though there be practically no real cancellation. Consider, for example, the extreme case where identical patterns of the same phase are recorded at two loci with one twenty times the other. This is certainly a case of no cancellation yet one which would yield a 0.1 coefficient by the above criterion.

While no entirely adequate criterion has been found, we have settled upon one which properly emphasizes the desirable cancellation feature irrespective of the absolute and relative sizes of the two components but which does not correct for the expected exaggeration of errors due to constant central terminal error. To form this coefficient we take the total magnitude of the reference component R and multiply it by the dividing ratio of the balance potentiometer in giving us Rn as the absolute voltage contributed at the movable potentiometer tap from the reference source. Similarly we get the corresponding absolute search voltage component by multiplying the total search magnitude S by $(1 - n)$ to yield $S(1 - n)$. As the noncancelling parts of these two potentials are presumably independent, we regard the sum of the two components at the potentiometer tap $Rn + S(1 - n)$ as the total potential present for complete non-cancellation. We now form the fraction

$$\frac{r}{Rn + S(1 - n)}$$

where r is the residual magnitude, and we use this fraction as our test criterion.

It is evident that this quantity which we call C (for cancellation coefficient) can only take values between zero and unity so that a good cancellation will give a C approaching zero, a bad one a C approaching one. While this coefficient C is statistically not a direct measure of nondipole component, it is more representative on the average than any other simple measure which we have been able to devise.

There is a pitfall against which we must guard and into which some of those working in this field may inadvertently have fallen. This is the realm of what we call "false" mirror patterns. When electrocardiograms are taken at a large

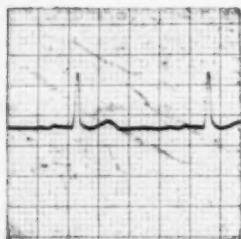
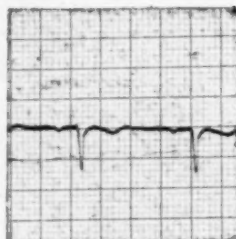
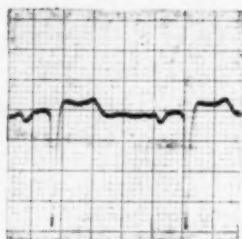
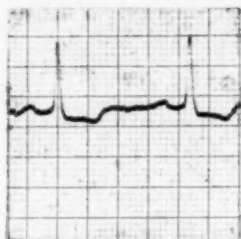
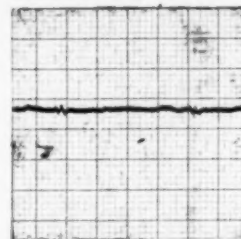
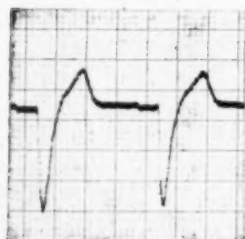
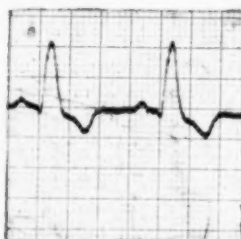
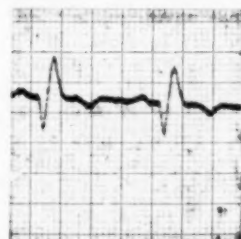
TRUE MIRROR PATTERNS**EXCELLENT CANCELLATION****REFERENCE****SEARCH****CANCELLATION****TRUE MIRROR PATTERNS****GOOD CANCELLATION****REFERENCE****SEARCH****CANCELLATION****FALSE MIRROR PATTERNS****LITTLE CANCELLATION****REFERENCE****SEARCH****CANCELLATION**

Fig. 3.—Many apparent mirror patterns are really false mirror patterns differing slightly in phase or in relative scale of features. In the top group are shown records from a normal individual recorded between positions IV_4 for the reference and $IV_{10.5}$ for search with potentiometer ratio 42 per cent. The cancellation is seen to be nearly perfect and is recorded as 0.03. The positions are described in the second paper of this series.¹⁰ This middle group of patterns are for a patient with left ventricular strain. The records are between position III_{12} reference and $VI_{1.5}$ search with potentiometer ratio 29 per cent and cancellation coefficient 0.09. Despite the large contributing potentials, only a small residual is present. The bottom group of records are for a patient with left bundle branch block. The recordings were taken between V_2 reference and $II_{1.5}$ search with a potentiometer setting of 19 per cent. The reference pattern was recorded at one-half sensitivity because of its large amplitude. While the patterns look deceptively similar, their cancellation pattern is very large.

number of points on the surface of the body and are arranged into an anatomic map¹⁰ it is at once obvious that there is a tendency toward mirror patterns; that is to say, patterns from a point on the body referred to a central terminal tend to look like reversed images at different amplification of those obtained at an opposite point. Examples of such patterns are shown in Fig. 3. It is often impossible even by careful measurement to tell whether these are, or are not, true mirror images because even a millisecond or two difference in timing will make a vast difference in the cancellation coefficient. Unless each phase of the pattern coincides exactly with that of its image, they are not real mirror patterns and evidently did not result from the same complex of action currents except insofar as the reactive components of body impedance might have distorted them. Patterns which have similar shapes but in which various features are slightly different in proportional size form particularly deceptive false mirror patterns. Figure 3 shows typical true and false mirror patterns with cancellation coefficients ranging between 0.03 and 0.6. Even for this last glaringly false mirror pattern, the search and reference patterns look much alike. It is therefore necessary to prove not only wave form but also exact phase to better than a millisecond before potentials can be regarded as true mirror images.

Our method of analysis obviously gives heaviest emphasis to the QRS complex as the P and T are usually smaller in magnitude and therefore seldom dominate the residual. While it is perfectly possible to analyze these portions of the electrocardiogram selectively, we have not yet done so. It is probable that this work would be difficult and tedious because of the low potentials which would have to be measured. We have, however, observed that the T cancellation often occurs at a slightly different locus than the QRS and that in certain cases of heart disease the difference becomes exaggerated.

SUMMARY

1. A theoretical analysis is made of the mirror image electrocardiograms which are often found at anatomically opposite positions across the heart.
2. A cancellation technique is proposed whereby similar parts of presumed mirror patterns are cancelled leaving only the unbalanceable portion as a residual.
3. A cancellation coefficient has been devised which permits quantitative evaluation of mirror pattern excellence.
4. Use of a polar cardioscope is proposed for detailed study of electrocardiographic patterns over a lengthy observation period and is found valuable experimentally.
5. A double exposure photographic method is utilized to establish cancellation axes visually within the body.
6. The existence of deceptive "false" mirror patterns is pointed out and demonstrated.
7. The importance of exact phase coincidence for cancellation is emphasized.
8. True mirror patterns of good cancellation excellence are not rare and most patterns have good mirror images, but some noncancellable patterns are found.

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THE DIAGNOSIS OF INFARCTION OF THE INTERVENTRICULAR SEPTUM

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THE accuracy of electrocardiographic diagnosis and localization of myocardial infarction has been advanced recently through the use of unipolar extremity and multiple precordial leads. Diagnostic criteria have been established which permit improved topographical localization of infarcted area. However, relatively little attention has been given to the electrocardiographic diagnosis of infarction of the interventricular septum; the frequent occurrence and diagnostic features of this condition are not generally appreciated. The present study seeks to clarify the diagnosis by an analysis of electrocardiographic observations in a group of cases with carefully documented septal infarctions.

MATERIALS AND METHODS

This study is based on all cases of myocardial infarction observed at the Beth Israel Hospital during the years 1946 and 1947 in which adequate electrocardiographic and pathologic data were available. These were thirty-five in number. Adequate pathologic examination comprised the Schlesinger method of injection plus dissection of the coronary arteries,¹ gross examination of the epicardium, myocardium, endocardium, and valves, and histologic examination of multiple sections of the myocardium. Adequate electrocardiographic data consisted of one or more 12 lead electrocardiograms (3 standard, 6 unipolar precordial, and 3 augmented unipolar extremity leads), taken shortly before death. In most cases serial electrocardiograms had been obtained during the terminal illness.

The pathologic data were analyzed and classified as outlined below, and electrocardiographic-pathologic correlations were made. The hearts were divided into two groups on the basis of whether or not infarction involved the septum. Those with septal infarction were subclassified according to the extent of septal involvement. They were graded as "massive" when approximately one-half or more of the septal muscle was infarcted, "minimal" when only a few tiny patches of infarction were present, and "moderate" when the degree of involvement fell between these two extremes.

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RESULTS

Pathologic Findings.—Septal involvement was present in thirty-two of the thirty-five cases of myocardial infarction. It was classified as massive in ten cases, moderate in twelve, and minimal in the remaining ten cases. The left ventricular side of the septum was invariably involved, regardless of the extent of septal infarction. Involvement of the free ventricular wall was present in every case. In fact, twenty-five of the thirty-two hearts, including twenty of the twenty-two with massive and moderate septal infarction, had involvement of both anterior and posterior walls, although not necessarily of the same age. Of the ten cases with minimal septal involvement, five had anterior and posterior infarction, but in three of these the lesions consisted of scattered miliary areas of necrosis. None of the anterior and posterior infarctions in the massive and moderate groups were of the miliary type. Infarction of both anterior and posterior walls was not present in any of the three cases without septal involvement. Severe atherosclerosis with multiple occlusions and narrowings was the rule in all cases; the main stems or major branches of both coronary arteries were frequently occluded.

Acute infarction was present in every case with massive septal involvement; while there were many instances of healed infarction in the moderately and minimally infarcted septa, no healed massive septal infarcts were encountered. Perforation of the septum was not observed in this group.

Electrocardiographic Findings.—The outstanding electrocardiographic finding in the cases with septal infarction was defective conduction. Table I summarizes the relationship between the conduction defects and the extent of septal infarction. It will be noted that conduction defects were present in seven of the ten cases with massive infarction of the septum, in seven of the twelve with moderate infarction, and in five of the ten cases with minimal infarction of the septum. There were no conduction defects in the three cases of infarction without septal involvement.

There were four cases with complete bundle branch block in the group with massive infarction (ten cases), one left, two right, and one with both left and right. Serial electrocardiograms in the latter case showed alternating left and right bundle branch block, then transient complete auriculoventricular block, followed by alternating left and right bundle branch block, and finally left bundle branch block which persisted until death. Complete auriculoventricular block was observed in two additional cases, and prolongation of the P-R interval in two cases, one of which also displayed left bundle branch block.

In the group with moderate septal infarction (twelve cases) there were three instances of complete left bundle branch block, two of incomplete left bundle branch block, one of incomplete right bundle branch block, and one of intra-ventricular block of undetermined type. The electrocardiogram in the latter case displayed the characteristic features of acute posterior myocardial infarction. The QRS complex measured 0.12 second, and was suggestive but not diagnostic

TABLE I. RELATIONSHIP BETWEEN CONDUCTION DEFECTS AND EXTENT OF SEPTAL INFARCTION. THE APPARENT DISCREPANCIES IN THE CASE TOTALS ARE DUE TO THE FACT THAT SEVERAL CASES EXHIBITED MORE THAN ONE CONDUCTION DEFECT

CONDUCTION DEFECTS	EXTENT OF SEPTAL INFARCTION				TOTAL
	MASSIVE 10 CASES	MODERATE 12 CASES	MINIMAL 10 CASES	NONE 3 CASES	
Intraventricular Block					
Bundle Branch Block					
Left BBB	1	3	0	0	4
Right BBB	2	0	0	0	2
LBBB and RBBB	1	0	0	0	1
Incomplete Bundle Branch Block					
Left	0	2	1	0	3
Right	0	1	1	0	2
Type Undetermined (?RBBB)	0	1	0	0	1
Arborization (Peri-infarction) Block	0	0	1	0	1
Auriculoventricular Block					
Complete Auriculoventricular Block	3	1	0	0	4
3:2 Auriculoventricular Block	0	1	0	0	1
Wenckebach Phenomenon	0	0	1*	0	1*
Prolonged P-R Interval	2	1	1*	0	4
Total Cases	7	7	5*	0	19*

*Two cases of partial auriculoventricular block probably due to overdigitalization.

of right bundle branch block. Serial tracings showed auriculoventricular nodal rhythm with retrograde conduction, transient 3:2 auriculoventricular block, and finally complete auriculoventricular block. Prolongation of the P-R interval was present in one of the cases with left bundle branch block.

In the group with minimal infarction (ten cases) there was one instance of incomplete left bundle branch block, one of incomplete right bundle branch block, and one of "arborization" or "peri-infarction" block. In addition, there was one instance of prolongation of the P-R interval and one of partial auriculoventricular block with Wenckebach periods, both in patients who received excessive amounts of digitalis.

Complete Left Bundle Branch Block.—Pathologic studies in one of the five cases of complete left bundle branch block showed recent massive transmural infarction of the entire septum, a large recent posterior wall infarction, and a tiny fibrotic anterior apical lesion. Serial electrocardiograms revealed alternating left and right bundle branch block followed by other conduction defects as noted above. Tracings showing otherwise typical features of left bundle branch block exhibited Q waves in the left precordial leads.

The remaining four cases of left bundle branch block showed healed septal infarction, with superimposed massive acute septal infarction in one case. Histologic study of the latter revealed massive transmural infarction of the anterior and lateral left ventricle extending in patchy fashion

to the posterior left and right ventricles and septum. In addition, there was patchy fibrosis of the septum and adjacent portions of the left ventricle anteriorly and posteriorly, with an area of gross fibrosis of the posterobasal quadrant of the septum. Acute infarction of the septum was most marked in the posterior one-half from apex to base, where it was transmural in several areas. Electrocardiograms obtained several months prior to the final illness exhibited P-R interval prolongation (0.23 second), a QRS interval of 0.09 second with features characteristic of left ventricular hypertrophy, and precordial Q waves consistent with old anterior infarction. During the terminal episode of myocardial infarction the electrocardiogram showed extremely low voltage in the limb and left precordial leads, a QRS complex of 0.12 second, and the characteristic features of left bundle branch block. The P-R interval remained unchanged and the precordial Q waves disappeared. The onset of left bundle branch block and low voltage in this case coincided with massive acute infarction of the septum and a considerable portion of the left ventricle.

The pathologic and electrocardiographic findings in two of the three remaining cases of left bundle branch block were generally alike. Both showed widespread old infarction of the left ventricle (with aneurysm formation in one case), and patchy fibrosis of the left ventricular side of the septum. Electrocardiograms showed left bundle branch block with low voltage in the limb and left precordial leads. P-R interval prolongation (0.26 second) was present in one case. As in the previous case, left bundle branch block and low voltage were associated with extensive infarction of the left ventricle and septum.

The remaining case had an old transmural anterior apical infarct extending into the subendocardial layers of the septum. The septal lesion was limited to the subendocardial zone on the left side, and extended as a dense fibrous band over the anterior three-fourths of the septum from apex to base. There was also patchy fibrosis of the remainder of the left ventricular side of the septum. Electrocardiograms revealed auricular fibrillation and left bundle branch block with a QRS interval of 0.18 second.

The usual electrocardiographic signs of myocardial infarction were lacking in the tracings which displayed left bundle branch block, except as noted in the first case above.

Incomplete Left Bundle Branch Block.—Incomplete left bundle branch block was present in three cases. The septal lesion consisted of patchy fibrosis and acute necrosis involving all regions of the left ventricular side of the septum in one case, and gross fibrous replacement of the apical two-thirds with patchy fibrosis of the basal one-third of the left ventricular side of the septum in another. In the third case, there were only scattered patches of fibrosis of the left ventricular aspect of the septum. Low voltage was present in all leads in the first case.

Complete Right Bundle Branch Block.—Right bundle branch block was encountered in three cases, once in association with left bundle branch block and complete auriculoventricular block, and twice as the sole conduction disturbance. The pathologic findings in the first case have been described above in the discussion of left bundle branch block and included massive transmural infarction of the entire septum. In the tracings showing right bundle branch block, the diagnosis of septal infarction was suggested by the finding that the initial upward deflections in the right precordial leads, presumably of septal origin, were replaced by Q waves.

In the second case, there was patchy transmural acute infarction of the entire septum, the entire left ventricle except for the basal anterolateral segment, and scattered patches of the posterior right ventricle. The initial electrocardiogram showed normal conduction and evidence of acute antero-septal infarction. A subsequent tracing revealed right bundle branch block with prominent Q waves in all precordial leads.

Pathologic study of the third case revealed acute anterior infarction with transmural involvement of the entire septum. The electrocardiogram exhibited right bundle branch block, and Q waves, elevated S-T segments, and inverted T waves in the right precordial leads.

It is noteworthy that in all three cases, septal infarction was massive and transmural, in contrast to those cases of left bundle branch block with infarction limited to the left side of the septum.

Incomplete Right Bundle Branch Block.—Incomplete right bundle branch block was the sole conduction disturbance in two cases. Extensive transmural acute infarction of the anterior left ventricle with aneurysm formation was present in one case. The lesion extended in patchy fashion into the anterior one-half of the septum from base to apex, but was limited to the left

ventricular side. Serial electrocardiograms displayed incomplete right bundle branch block and QRS and S-T-T changes characteristic of acute infarction in all six precordial leads.

In the second case, there was a healed posterolateral infarct with superimposed acute miliary infarction, largely subendocardial, scattered over the entire left ventricle except for the basal portion anteriorly. Scattered patches of fibrosis and acute miliary infarction involved the left ventricular side of the septum. The electrocardiogram showed incomplete right bundle branch block, Q waves in Leads III and aV_F, and S-T segment depression in Leads I, II, and the precordial leads.

Intraventricular Block of Undetermined Type.—Pathologic studies in the case of intraventricular block of undetermined type mentioned above revealed a small healed anterior apical infarct and a massive acute transmural infarct of the posterior wall of the left ventricle and the entire right ventricle. The acute infarct extended across the apical one-third of the septum and a narrow zone of the posterobasal region adjoining the posterior wall. The initial electrocardiogram showed auriculoventricular nodal rhythm with retrograde auricular conduction; a QRS interval of 0.12 second; broad deep Q waves, elevated S-T segments and inverted T waves in Leads II, III and aV_F; small R waves, broad deep S waves with slurred upstrokes, and tiny R' deflections in the right precordial leads; and tiny Q waves, tall R waves, and broad shallow S waves in Lead I and the left precordial leads. The late R' deflections in the right precordial leads were much smaller than those usually seen in right bundle branch block. The possibility exists, however, that right bundle branch block was present, and that the R' deflections were unusually small, owing to the extensive infarction of the right ventricle. Subsequent electrocardiograms revealed 3:2 auriculoventricular block and, terminally, complete auriculoventricular block (see *Complete Auriculoventricular Block*.)

Arborization (Feri-infarction) Block.—Arborization¹⁰ or peri-infarction block¹¹ was observed in one case. Pathologic studies revealed a fibrotic transmural infarct of the apical one-half of the anterior and lateral walls of the left ventricle, merging laterally with a healing subendocardial infarct of the lateral and posterobasal walls. Septal involvement was minimal, being limited to a few scattered patches of necrosis of the left ventricular side. Serial electrocardiograms were characterized by a QRS duration of 0.12 second, broad deep Q waves followed by late R waves in Leads II, III, aV_F and V₃ to V₆, elevated S-T segments and inverted T waves initially in the left precordial leads and subsequently in Leads II, III, and aV_F.

Complete Auriculoventricular Block.—Complete auriculoventricular block was observed in four cases, all with acute infarction of the posterobasal region of the septum extending from the posterior wall or from both posterior and anterior walls. In one case, the block was preceded by alternating left and right bundle branch block; in another it followed an undetermined type of intraventricular block; in the remaining two it was the sole conduction defect. The block was transient in the first case, and appeared during the last day of life in the other three. High grade auriculoventricular block associated with healed septal infarction was not observed.

Conduction Defects with Additional Features.—Several of the cases with intraventricular conduction defects exhibited additional findings of interest. Four cases of complete or incomplete right bundle branch block had anterior wall and septal infarction, and showed broad, deep Q waves in the right precordial leads. The single case of incomplete right bundle branch block with posterior wall and septal infarction exhibited an abnormal Q wave in the left leg lead. Four of the eight electrocardiograms with complete or incomplete left bundle branch block displayed abnormally low voltage in the limb and left precordial leads. Extensive infarction of the septum and anterior and posterior walls of the left ventricle was present in each case. A fifth case with left bundle branch block and anterior wall and septal infarction exhibited Q waves in Leads V₃ and V₆.

Age of Septal Infarction.—Table II correlates intraventricular conduction defects and the age of septal infarction. It will be seen that complete auriculoventricular block and right bundle branch block were encountered only in cases with acute septal infarction.

Location of Septal Infarction.—The relationship between intraventricular conduction disturbances and the location of septal infarction is shown in Table III. The incidence and types of conduction defects were essentially similar whether the infarct extended from the anterior or posterior wall into the septum, or from one wall across the entire septum to the opposite wall.

TABLE II. RELATIONSHIP BETWEEN CONDUCTION DEFECTS AND AGE OF SEPTAL INFARCTION.
NOTE THAT COMPLETE AURICULOVENTRICULAR BLOCK AND COMPLETE RIGHT BUNDLE
BRANCH BLOCK WERE OBSERVED ONLY IN ASSOCIATION WITH
ACUTE SEPTAL INFARCTION

CONDUCTION DEFECTS	AGE OF SEPTAL INFARCTION			TOTAL
	ACUTE 11 CASES	OLD 12 CASES	ACUTE AND OLD 9 CASES	
Intraventricular Block				
Bundle Branch Block				
Left	0	3	1	4
Right	2	0	0	2
LBBB and RBBB	1	0	0	1
Incomplete Bundle Branch Block				
Left	0	2	1	3
Right	0	1	1	2
Type Undetermined (? RBBB)	1	0	0	1
Arborization (Peri-infarction) Block	1	0	0	1
Auriculoventricular Block*				
Complete Auriculoventricular Block	4	0	0	4
3:2 Auriculoventricular Block	1	0	0	1
Prolonged P-R Interval*	0	1	2	3
Total Cases**	7	6	4	17*

*Excluding two cases of partial auriculoventricular block due to overdigitalization.

**Several cases had more than one conduction defect.

All of the cases of complete bundle branch block had infarction, either confluent or patchy, along the entire length of the septum from apex to base. In the case of intraventricular block of undetermined type, there was transmural infarction of the apical one-third and a narrow posterobasal zone of the septum. The extent of involvement in the cases with incomplete bundle branch block varied from scattered patchy fibrosis to infarction of the left ventricular side of the septum from apex to base.

Infarction of the left ventricular side of the septum was present in every case and therefore in all cases with left bundle branch block; one case of the latter had transmural infarction. All three cases with complete right bundle branch block had involvement of the right as well as the left ventricular side of the septum; that is, transmural infarction.

The hearts in the cases with auriculoventricular block (excluding the two cases associated with overdigitalization) showed posterior wall infarction extending into the septum in each instance with or without involvement of the anterior wall as well (Table IV). In three cases with complete auriculoventricular block, extensive infarction of virtually the entire septum (including the posterobasal region) was present, while the fourth showed infarction limited to the apical one-third and a small posterobasal area adjacent to the posterior wall. The latter case exhibited transient partial (3:2) auriculoventricular block prior to the development of complete auriculoventricular block. There were three instances of prolongation of the P-R interval (0.23 to 0.26 second), two of which were associated with left bundle branch block. Massive acute and healed septal infarction was present in two cases, and moderate patchy fibrosis of the left ventricular side of the septum in the third; the posterobasal area was involved in all three.

Miscellaneous Observations.—While infarction, old or acute, of both anterior and posterior walls was present in twenty-five of the thirty-two cases with septal infarction, diagnostic electrocardiographic evidence of both anterior and posterior infarction was found in only five cases, and

TABLE III. RELATIONSHIP BETWEEN INTRAVENTRICULAR CONDUCTION DEFECTS AND LOCATION OF SEPTAL INFARCTION. THE SECTION DESIGNATED "LOCATION OF INFARCT" INDICATES WHETHER THE SEPTAL LESION EXTENDED TO THE ANTERIOR OR POSTERIOR WALL OR BOTH. IT DOES NOT REFER TO ADDITIONAL LESIONS OF THE FREE WALL WHICH WERE NOT CONFLUENT WITH THE SEPTAL INFARCT.

CONDUCTION DEFECTS	LOCATION OF INFARCT			THICKNESS OF SEPTUM INFARCTED		APICAL-BASAL EXTENT		
	ANTERIOR WALL AND SEPTUM	POSTERIOR WALL AND SEPTUM	ANT. AND POST. WALLS AND SEPTUM	TRANS-MURAL	LV SIDE ONLY	APEX TO BASE	APICAL 1/3 AND BASE	SCATTERED PATCHES
LBBB (4 cases)	1	1	2	1	3	4	0	0
Inc. LBBB (3 cases)	2	0	1	0	3	2	0	1
RBBB (2 cases)	1	0	1	2	0	2	0	0
Inc. RBBB (2 cases)	1	1	0	0	2	1	0	1
LBBB and RBBB (1 case)	0	1	0	1	0	1	0	0
Intravent. Block (1 case)	0	1	0	1	0	0	1	0
Arboriz. Block (1 case)	0	1	0	0	1	0	0	1
Total	5	5	4	5	9	10	1	3

TABLE IV. RELATIONSHIP BETWEEN AURICULOVENTRICULAR BLOCK AND LOCATION OF SEPTAL INFARCTION. THE POSTEROBASAL REGION OF THE SEPTUM WAS INVOLVED IN ALL CASES, WITH EXTENSION TO THE POSTERIOR WALL OR TO BOTH POSTERIOR AND ANTERIOR WALLS. (SEE TEXT)

CONDUCTION DEFECTS	ANTERIOR WALL AND SEPTUM	POSTERIOR WALL AND SEPTUM	ANTERIOR AND POSTERIOR WALLS AND SEPTUM
Complete Auriculoventricular Block (4 Cases)	0	2	2
3:2 Auriculoventricular Block (1 Case)	0	0	1
Prolonged P-R Interval (3 Cases)	0	2	1

suggestive evidence in six others; eight of the eleven were cases with massive or moderate septal involvement. Seven cases had acute infarction of the septum and adjacent areas of the anterior and posterior walls, but only two of these exhibited the electrocardiographic signs of simultaneous acute anteroseptal and posterior infarctions.

Electrocardiograms displaying normal conduction with QS deflections and abnormally elevated S-T segments in right precordial leads were observed in eight of the thirty-five cases of myocardial infarction. Considerable septal infarction was present in seven, but the remaining case had anterior wall infarction without extension to the septum.

Disturbances in rhythm were observed nine times in eight cases with septal infarction. There were three instances of paroxysmal ventricular tachycardia, two of auricular fibrillation, three of paroxysmal supraventricular tachycardia, and one of auriculoventricular nodal rhythm. No correlation was apparent between the arrhythmias and septal infarction. In three cases, the arrhythmias occurred in the absence of acute septal involvement (that is, old septal infarction and acute infarction of the free wall were present).

DISCUSSION

Incidence of Septal Infarction.—The incidence of septal infarction observed in this series represents the frequency of septal involvement among cases of myocardial infarction coming to autopsy in a general hospital. It does not, therefore, apply to nonfatal myocardial infarction or to myocardial infarction in general. Some degree of septal involvement, including tiny lesions of questionable significance, was present in thirty-two, or 91 per cent of the thirty-five cases. Moderate or massive septal infarction was present in twenty-two, or 63 per cent. The latter compares with an identical figure reported by Myers and associates² and with 55 per cent and 57 per cent observed by Littmann³ and Master and associates,⁴ respectively.

Mortality Rate.—The absence of healed massive infarction in this series suggests that survival is uncommon in the presence of extensive septal infarction. Others have pointed out the increased mortality rate associated with myocardial infarction complicated by intraventricular and high-grade auriculoventricular conduction defects.^{5,6} Littmann estimated the mortality of extensive septal infarction at about 70 per cent, and pointed out that this might be largely due to widespread myocardial destruction rather than to septal infarction per se.³

Conduction Defects.—The coexistence of septal infarction and conduction disturbances does not necessarily establish a cause and effect relationship. It is generally known that conduction defects may exist in the absence of septal in-

farction; our observations, and those of others, indicate that extensive septal infarction may exist without leading to disturbed conduction. Nevertheless, the anatomic location of the intraventricular conduction system suggests a possible relationship between septal lesions and defective conduction; this is supported by animal experiments. Master and associates observed that intraventricular conduction defects were twice as frequent in infarctions involving the septum compared to those sparing the septum, and that septal involvement was present in four-fifths of the cases of myocardial infarction displaying defective intraventricular conduction,⁵ and in most cases showing high-grade auriculoventricular block.⁶

The hearts from the five cases with complete, and from the three cases with incomplete left bundle branch block all showed septal infarction. In one of the latter, only scattered patches of fibrosis in the left ventricular aspect of the septum were noted, suggesting independence of the conduction disturbance and the observed lesion. Extensive infarction of the major portion of the left ventricle may account for the low voltage observed in four of the cases with complete or incomplete left bundle branch block. The presence of Q waves in left precordial leads exhibiting otherwise typical features of complete left bundle branch block, as noted in one of our cases, has been commented upon by others. It has been attributed to septal infarction with transmission of initial negative potentials from the right ventricular cavity to the left precordium.⁷⁻⁹

The massive and transmural septal infarction found in the three cases with complete right bundle branch block is of considerable interest. Review of the cases reported in detail by Myers and associates² revealed similar findings in their cases with right bundle branch block and septal infarction. However, this was not observed by Littmann³ or by Somerville and Wood⁸ in smaller series with less detailed pathologic documentation. There was no clear relationship between the incomplete right bundle branch block observed in two of our cases, and the associated histologic findings.

It will be noted that QRS changes diagnostic of infarction were present in all three cases of right bundle branch block, but in only one of five with left bundle branch block (Q waves in left precordial leads).

The conduction disturbance referred to above as "arborization block" was probably related to delay of the impulse in the densely infarcted subendocardial region, and therefore unrelated to septal infarction. It should be noted that the latter was minimal.

It is apparent that complete auriculoventricular block complicating myocardial infarction is usually associated with infarction of the posterobasal region of the septum. This presumably interrupts conduction through the bundle of His, although complete auriculoventricular block could result from simultaneous block of both bundle branches, a possibility in the first case mentioned above. The correlation between acute posterobasal septal infarction and complete auriculoventricular block has been noted by others.^{2,6} The finding that high-grade auriculoventricular block is usually transient or soon followed by death is also in agreement with previous studies.^{6,12}

P-R interval prolongation in three cases of this series was observed to persist from eight days to six months. Posterobasal septal infarction was present in all three. However, since it was not possible to ascertain whether the conduction delay antedated or coincided with the infarction, it was not clear whether any cause and effect relationship existed between the two.

Anterior and Posterior Infarction.—Roesler and Dressler¹³ have suggested that extensive septal infarction be considered when the electrocardiogram shows evidence of simultaneous acute or subacute posterior and anteroseptal infarction. They observed such a pattern in five cases with extensive septal infarction extending from adjacent anterior and posterior ventricular walls. They pointed out, however, that a similar pattern may sometimes be seen when there is apical infarction extending anteriorly and posteriorly. Littmann³ made similar observations, but concluded that conduction disturbances were more characteristic of septal infarction.⁸ In the present study, electrocardiographic signs of simultaneous acute anteroseptal and posterior infarction were encountered only twice, although there were seven cases in which histologic examination revealed acute infarction in the septum and adjacent anterior and posterior walls. It is clear from our observations that concomitant infarction, regardless of age, of both anterior and posterior walls is much more commonly associated with septal infarction than would be suspected from the electrocardiographic evidence.

QS Deflections in Right Precordial Leads.—Myers and associates² have stated that QS deflections with elevated S-T segments in leads facing the right side of the septum are attributable to septal infarction, the latter permitting transmission of left ventricular cavity potentials to the right precordium. Leads in which an intrinsicoid deflection was present in the P wave were considered to be in the vicinity of the right atrium and therefore facing the right side of the septum. As noted previously, this pattern was observed in eight cases of the present series, seven of which had considerable septal infarction. In the eighth case, however, infarction was limited to the anterior wall adjacent to the septum, the latter being spared. Evidently, QS deflections and elevated S-T segments in the right precordial leads are usually associated with septal infarction, but may occur even though the septum is free of histologically detectable necrosis.

SUMMARY

Thirty-five cases of myocardial infarction have been studied with particular emphasis on the pathologic and electrocardiographic correlations in those with septal involvement. The hearts were examined by the Schlesinger method of injection plus dissection supplemented by multiple microscopic sections of the myocardium.

Septal involvement was present in thirty-two, and was considerable in twenty-two of the cases. Septal lesions were always associated with infarction of the free wall anteriorly or posteriorly. In twenty-five of the thirty-two cases with septal involvement, infarction of both anterior and posterior walls was present. The left ventricular side of the septum was invariably affected; ex-

tension to the right ventricular side (that is, transmural septal infarction) was present in five cases. It is probable that massive septal infarction is usually fatal, since no healed case of this type was encountered.

Conduction defects were the most common electrocardiographic findings in cases with septal infarction. The development of bundle branch block or high-grade auriculoventricular block during the course of myocardial infarction was always correlated with acute septal infarction. Complete left bundle branch block was associated with moderate or massive septal infarction in five cases. Low voltage in the limb and left precordial leads was observed in three of these; at autopsy extensive infarction of the left ventricle was present. Q waves were present in the left precordial leads of one case of left bundle branch block associated with massive septal infarction. Incomplete left bundle branch block occurred in two cases with moderate septal infarction, and in one with minimal septal involvement. Low voltage was present in one of the former, and was associated with extensive infarction of the left ventricle.

Complete right bundle branch block and septal infarction were observed in three cases. It is worthy of note that extensive and transmural septal infarction was present in all three, and all showed prominent Q waves in the right precordial leads. Incomplete right bundle branch block with Q waves in the right precordial leads was encountered in one case with moderate infarction limited to the left side of the septum and massive anterior wall infarction. Another case showed incomplete right bundle branch block with Q waves in Leads III and aV_F associated with posterior wall infarction and minimal septal involvement.

An unidentified type of intraventricular block, probably representing right bundle branch block complicated by right ventricular infarction, preceded the development of complete auriculoventricular block in one case with moderate septal infarction. In another case with minimal septal involvement the electrocardiogram displayed the features described as characteristic of arborization peri-infarction block.

High-grade auriculoventricular block was observed in four cases with acute infarction of the posterobasal region of the septum. This defect was transient, or was a terminal event. P-R interval prolongation was present in three cases.

It was felt that the observed septal lesions could reasonably account for the disturbed conduction in the cases of complete bundle branch block and high-grade auriculoventricular block. No clear relationship could be discerned, however, in the cases of incomplete right bundle branch block, arborization block, and P-R interval prolongation, and in one of the cases of incomplete left bundle branch block.

Electrocardiographic evidence of simultaneous acute antero-septal and posterior infarction was present in two cases with septal involvement. Three others exhibited diagnostic signs and six showed suggestive signs of anterior and posterior infarctions of varying ages. Thus, electrocardiograms disclosed evidence of both anterior and posterior infarction in less than half of the cases with such lesions.

QS deflections with elevated S-T segments in right precordial leads were present in eight cases, seven of which had septal infarction.

CONCLUSIONS

1. Septal involvement of significant degree is common in myocardial infarction, and is frequently associated with certain electrocardiographic features. The most common of these are signs indicative of conduction defects.
2. Conduction defects are diagnostic of septal infarction under the following conditions: When (a) bundle branch block, or high-grade auriculoventricular block appears during the course of acute myocardial infarction. High-grade auriculoventricular block indicates involvement of the posterobasal region of the septum. (b) Complete right bundle branch block is associated with conspicuous Q waves in the right precordial leads. (c) Left bundle branch block is associated with Q waves in the left precordial leads. (d) Left bundle branch block is associated with low voltage in the limb and left precordial leads.
3. QS deflections with abnormally elevated S-T segments in the right precordial leads of electrocardiograms displaying normal intraventricular conduction are fairly reliable evidence of acute septal infarction. Occasionally, such tracings will occur in the absence of septal involvement.
4. A characteristic sign of septal infarction is electrocardiographic evidence of simultaneous acute anteroseptal and posterior infarction. However, this occurs relatively infrequently.
5. Electrocardiographic evidence of both anterior and posterior infarction, regardless of age, indirectly suggests the possibility of septal involvement.

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CLINICAL STUDIES ON PARASYSTOLE

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WHEN a focus in the auricles or the ventricles sends out stimuli independently from the normal pacemaker, an arrhythmia known as parasystole appears. All stimuli formed by these two centers, which fall outside the refractory phase, yield a response. Disturbances in the normal conduction system which lead to the appearance of two stimulus centers, as for example in complete heart block, are excluded from the definition of parasystole.

The automatic center may form stimuli at either a faster or slower rate than the normal pacemaker. If this automatic center is slower it has to be protected from the dominant center. If this were not the case it would be depolarized before sending out its own impulses. Conversely, when the ectopic center discharges at a faster rate a block must appear from time to time preventing the spread of the ectopic stimuli and permitting the normal pacemaker to come through. When there is no block an auricular or ventricular tachycardia is the consequence.

These two mechanisms of protection are called, respectively, protective and exit block. The word protective block is somewhat misleading because it does not mean a disturbance of conduction in the customary sense, but seems to be an inability of the parasystole center to respond to outside stimuli.^{3,8}

In order to establish the diagnosis of parasystole three main criteria are necessary:

1. Ectopic beats must be present with changing time in relation to the preceding beat of the basic rhythm.
2. A simple mathematical relationship between the interectopic intervals must exist, the intervals being a direct multiple of the shortest ectopic cycle length.
3. Combination beats due to the nearly simultaneous activation of the heart by the two centers of stimulus formation are seen.

In this report two instances of parasystole with unusual features are described.

Observation 1. An 88-year-old woman was admitted to the hospital because of congestive heart failure due to arteriosclerotic heart disease. On physical examination the essential findings were dullness on percussion and decreased breath sounds over the right base. Radiographic examination revealed a right pleural effusion. The heart was enlarged in all diameters and the

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aorta was tortuous and dilated. Blood pressure 210/110 mm. Hg. The laboratory data was not contributory. With digitalis and mercurials there was rapid improvement.

The first tracing obtained after admission is reproduced in Fig. 1. At the beginning of the tracings, in Leads I, II and V_2 a regular sinus rhythm appears with a rate of 88 beats per minute. The P-R interval is .20 second.* In the same leads after a few sinus beats a regular ventricular rhythm takes over. This ectopic rhythm has a rate of 79 beats per minute. The distance between the first ectopic and the preceding normal beat measures with uniformity .33 second. This fact is important, as it demonstrates that the first ectopic beat in each series maintains a fixed coupling to the last normal beat.

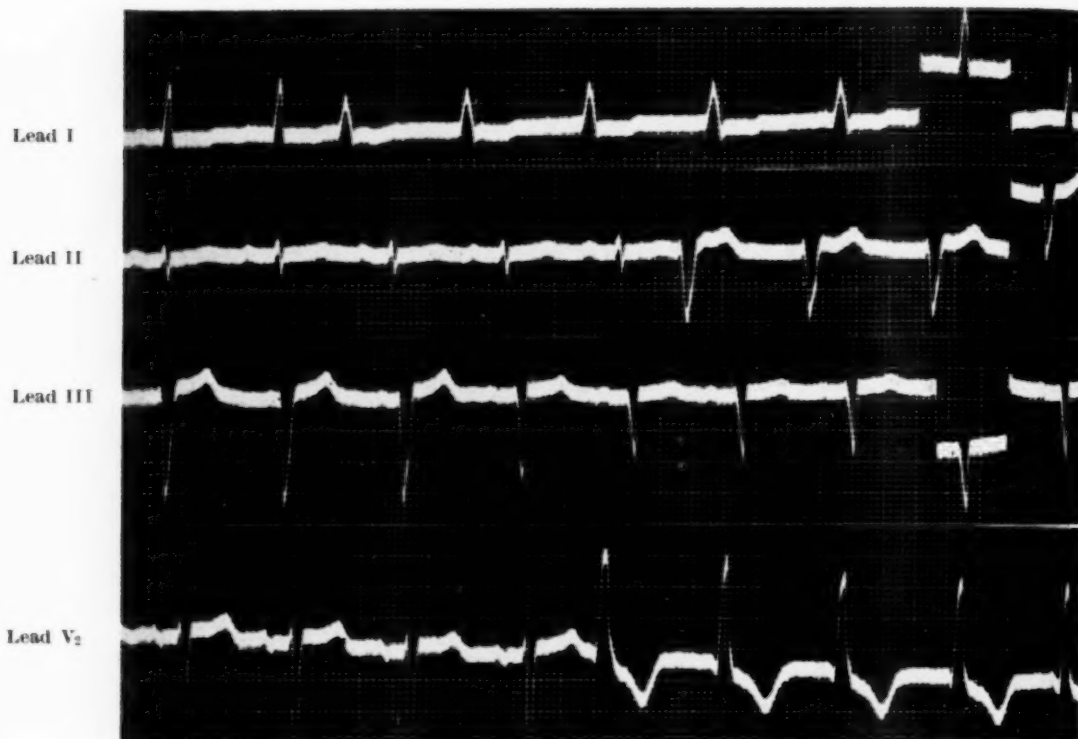


Fig. 1.—Leads I, II, V_2 , show after a few sinus beats in each lead an "intermittent parasystole," that is, a chain of ectopic ventricular beats with "fixed coupling" to the preceding sinus beat. Lead III shows the transition from the ectopic to the sinus rhythm. The first and second beats are ectopic, the third and fourth are combination beats followed by sinus beats.

When the ectopic rhythm becomes dominant, the auricles continue to beat at their original rate. Therefore the slight variations in the form of the ectopic complexes can be attributed to the P waves buried in the QRS-T complexes of these beats. In Fig. 1, Lead V_2 , a P wave immediately preceding the last ectopic QRS complex can be seen. The appearance of combination beats during the change from one rhythm to the other is to be expected, as the ectopic beats do not depolarize the sinus node by retrograde conduction to the auricles. These combination beats occur when the relation between the two impulses is such that they cause depolarization nearly simultaneously of the ventricles. This relation will occur more frequently as the difference in rate of the two foci decreases. Fig. 1, Lead III, shows the transition from the ectopic to the sinus rhythm. The first and second beats are ectopic, the third and fourth are combination beats, thereafter normal sinus beats appear.

*All these figures represent hundredths of a second.

Figure 2, *A* is a tracing from the same patient taken two days later in Lead II. The basic rhythm is a regular sinus rhythm with a rate of 82 beats per minute. This rhythm is interrupted at different intervals by ectopic ventricular beats identical to those described in Fig. 1. The intervals between these beats and the preceding sinus beats are respectively: 56, 32, 60, 36, 52, 31 hundredths of a second. This variable length of coupling proves, that we are not dealing with the usual type of extrasystoles. The shortest interval between two ectopic beats in a long tracing is the basis for the calculation of the rate of the ectopic rhythm. After three sinus beats the first ectopic beat appears. The distance to the next ectopic beat is 116 hundredths of a second, which is the shortest interectopic interval over long strips of tracing. The following interectopic interval measures 244 (2×116 plus 12), the next interectopic interval is again 116 hundredths of a second, the fourth is 362 (3×116 plus 14) the last is again 116 hundredths of a second. As compared with Fig. 1 obtained on the preceding day, the rate of the sinus as well as the ectopic rhythm has changed. The sinus rhythm changed from 88 to 82, the parasystolic rhythm from 79 to 51 beats per minute.

Figure 2, *B* represents Lead II during right carotid sinus pressure. Due to this pressure the sinus rhythm alternates with beats arising near the coronary sinus; the parasystolic beats have the same shape and form as described in Fig. 2, *A*. Subsequently the ectopic rhythm comes through alone, the sinus and atrioventricular rhythms being suppressed by vagal influence as a result of carotid sinus pressure. The interectopic cycle length is 122 hundredths of a second.

This case possesses certain features which are of special interest.

1. The ectopic rhythm as seen in Fig. 1 always begins with the first ectopic beat in the series showing fixed coupling to the preceding normal sinus beat.
2. Two days later ectopic beats of the same shape and form as seen in Fig. 1 are present, Fig. 2, *A*, but the coupling is not fixed, and the rate of the ectopic rhythm is slower; parasystole is present.
3. During carotid sinus pressure a pure ectopic rhythm is elicited, the basic rhythm being suppressed by increased vagal tone.

Observation 2. A 62-year-old woman came to the hospital because of rapidly developing ascites within the two weeks prior to admission; she also had several episodes of hematemesis during the same period. The past history was negative except for prolonged chronic alcoholism. Physical and radiographic examination failed to reveal any significant cardiac abnormality. The clinical diagnosis was chronic alcoholism and Laennec's atrophic cirrhosis.

The first electrocardiogram (Fig. 3, *A*) shows in Lead I a sinus rhythm with a rate of 86. (The ventricular complexes were normal in the standard leads and precordial Leads V_2 and V_4). The sinus rhythm is interrupted by abnormal ventricular complexes which appear at different intervals in diastole. Therefore there is no "fixed coupling" to the preceding sinus beat. The ectopic beats differ in shape depending on whether they are early or late in diastole. The third and fifth ectopic beats are pure ectopic beats, the first, second, and fourth are combination beats. The shortest interectopic interval consists of a combination beat and a pure ectopic beat; this interval measures 120 hundredths of a second. The interval between the first and second ectopic beats in Fig. 3, *A* measures 364 (3×120 plus 4), followed by an interval of 120, the third interectopic interval is 236 (2×120 minus 4) the last again 120 hundredths of a second. Therefore all three characteristic features of parasystole are seen—variable coupling, simple mathematical relationship between the interectopic intervals, and combination beats.

Figure 3, *B* reproduces a tracing in the same lead with right carotid sinus pressure. The arrows indicate beginning and end of right carotid pressure. At the beginning of the tracing two sinus beats appear followed during carotid sinus pressure by ten ectopic beats. The interectopic interval varies between 114 to 120 hundredths of a second. At the end of the strip the sinus beats reappear.

On re-examination one week later, no parasystole was found. However with carotid sinus stimulation it was elicited again. Figure 3, *C* shows this phenomenon. Three sinus beats with a

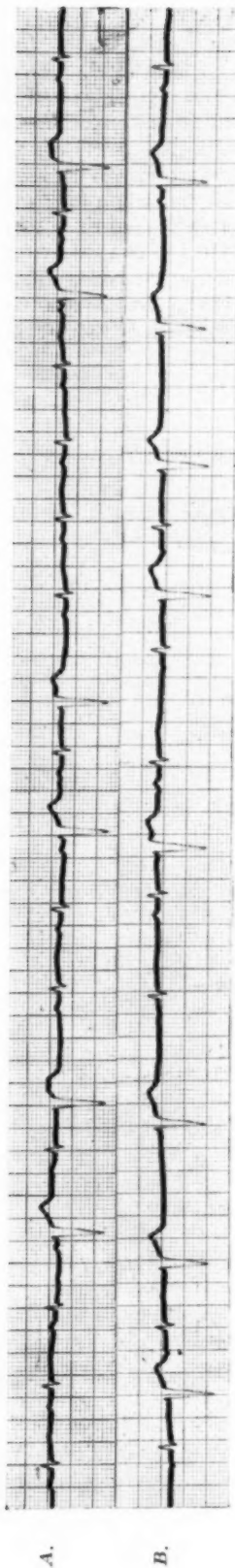


Fig. 2.—A shows the typical tracing of a parasystole. In B, during carotid sinus pressure, the normal pacemaker is slowed and atrioventricular beats appear. When the rhythm drops below 60 beats per minute the pure ectopic rhythm emerges.

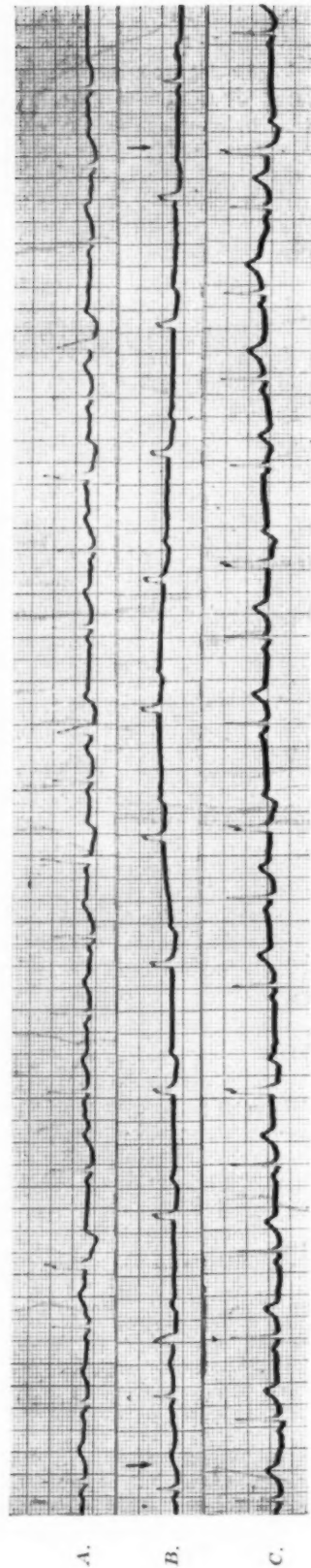


Fig. 3.—A demonstrates a typical tracing of a parasystole in Lead I. The first and fifth QRS complexes are pure ectopic beats, the first, second and fourth are combination beats. B, during carotid sinus pressure after two sinus beats a group of ten ectopic beats can be seen. C shows the tracing with the reappearance of the parasystole during carotid sinus pressure.

R-R interval of 74 are followed by two sinus beats with an R-R interval of 80 hundredths of a second. Then during carotid sinus pressure, the first ectopic beat of this series comes through. The interectopic intervals are 240 (2×120) 372 (3×120 plus 12) and 238 (2×120 minus 2) hundredths of a second. The couplings are: 56, 52, 56, 44, 38 hundredths of a second. This same stimulation (right carotid sinus pressure) was applied seven times in the next few days and each time it elicited a short parasystolic rhythm which disappeared within two to five beats after carotid sinus pressure was stopped.

The electrocardiograms of this patient present two unusual features:

1. Carotid sinus pressure allowed the parasystole rhythm to emerge for as long as ten ectopic beats.
2. Carotid sinus pressure caused the reappearance of the parasystole on seven consecutive instances.

DISCUSSION

The two observations presented above possess certain characteristics which are not seen in the classic parasystole tracings and which need therefore further explanation.

In the first case the ectopic center starts firing its own stimuli with "fixed coupling" to the preceding sinus beat. This can be explained in the following manner: the stimuli from the ectopic center are not strong enough to spread over the ventricles unless a stimulus can emerge during the supernormal phase of the preceding sinus beat.

With this first ectopic beat an ectopic tachycardia begins interrupted at various intervals by groups of regular sinus beats. In order for this phenomenon to appear the difference in the rate of the two centers must be relatively small, and the length of these groups increases as the difference decreases (in Fig. 1 the cycle length of the sinus rhythm is 72, of the parasystole rhythm 76). During the change to sinus rhythm, combination beats occur unless the ectopic center is in the atrioventricular node or in the common bundle.

The focus that produces this "intermittent parasystole"⁸ is the same, which two days later leads to the ventricular parasystole with simple interference, as can be seen by the identical shape of the QRS complexes (Fig. 2, A).

In the first case the calculated interectopic intervals are not always exactly a simple multiple of 116 hundredths of a second, the shortest interectopic interval. During the carotid sinus pressure we have in Fig. 2, B the possibility of measuring the "pure parasystolic cycle length," which is 122. This cycle length as the basis for the calculation demonstrates the exact mathematical relation of the interectopic interval ($244 = 2 \times 122$, $366 = 3 \times 122$). The fact that an interectopic interval which has interpolated sinus beats is occasionally shorter than that without sinus beats should be stressed at this point.¹³ The basis for this phenomenon is not known.

The two presented patients exhibit in their electrocardiograms during carotid sinus pressure a pure ectopic rhythm. In 1948 Vedoya et al¹³ reported an interesting observation in a 57-year-old woman with a past history of hypertension. Her electrocardiogram at first glance seemed to be essentially normal except for the occasional appearance of a premature atrioventricular nodal beat. The

authors noted that the coupling between the atrioventricular nodal beats and the preceding sinus beats revealed no definite mathematical relationship. This led them to suspect the existence of a parasystole and they recorded an electrocardiogram before and during carotid sinus pressure. Vagal stimulation inhibited the sinus node and a nodal rhythm emerged at the same rate as the calculated rate of the ectopic nodal rhythm, without interfering with the normal pacemaker thus allowing the atrioventricular nodal focus to command the beat of the heart. This is the first clinical report of an ectopic rhythm emerging during carotid sinus pressure. However, the fact that in our cases the focus is in the ventricle makes the differentiation between the two centers much more obvious. Scherf and Chick¹² postulated purely on a physiologic basis that the parasystolic rhythm without disturbance from the sinus rhythm could be obtained by vagal stimulation. This hypothesis was proved experimentally in the dog and the findings were identical with the clinical findings described above.

In the second patient carotid sinus pressure led to the reappearance of the parasystole at a time when only a regular sinus rhythm was present. To our knowledge it is the first time that this phenomenon was clinically seen. The appearance of a protective block during carotid pressure has been described (Scherf and Boyd, Fig. 213).⁸ Eckey² and Holzmann⁴ described the appearance of a parasystole after administration of strophanthin and experimentally Scherf and Chick¹¹ obtained the same result by cooling the sinus node.

This finding may be due to the chemical action of acetylcholine. That vagal stimulation is the trigger that sets off the arrhythmia is clearly seen in our tracings, as it disappears soon after the end of vagal influence and recurs at will with repeated vagal stimulation. Whether vagal fibers are present in the ventricles is still a matter of debate. However, vagal effects have been demonstrated in these chambers. These effects may be mediated by the release of acetylcholine in the auricles during vagal stimulation and absorbed by the ventricles through the coronary and thebesian vessels.⁶

It is well known that acetylcholine can have an excitatory action. In 1927 Wenckebach and Winterberg¹⁵ reported a case of paroxysmal ventricular tachycardia in which they were able to elicit short paroxysms of this arrhythmia by carotid sinus pressure. This effect could be elicited repeatedly. In 1950 Meredith and Beckwith⁵ reported two cases which manifested short attacks of paroxysmal ventricular tachycardia following carotid sinus pressure. In 1951 Blumenfeld and associates¹ reported a case in which carotid sinus pressure precipitated an attack of paroxysmal auricular tachycardia, whereas the same measure in the same patient readily abolished spontaneous attacks.

Experimentally it has been shown, that focal application of acetylcholine to the canine ventricle causes short runs of ventricular tachycardias.¹²

With the present knowledge of vagal influence on the heart it seems justified to state that the response to vagal stimulation may be variable, either depressing or stimulating, depending on the concentration of acetylcholine and the physiologic state of the responding cells.⁷

SUMMARY

1. The definition of the parasystole is reviewed and the criteria for the diagnosis of this arrhythmia are given.

2. Two cases of parasystole with unusual features are reported. These consist in appearance of the undisturbed ectopic rhythm during carotid sinus pressure in both patients and reappearance of parasystole during carotid sinus pressure in one patient. In one patient an ectopic ventricular rhythm with fixed coupling changed into a parasystolic rhythm spontaneously.

3. A discussion of vagal influence on this arrhythmia is presented.

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ECCENTRICITY AS A CAUSE FOR THE DIFFERENCE BETWEEN THE VECTORCARDIOGRAMS REGISTERED BY THE CUBE AND TETRAHEDRAL SYSTEMS

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THIS REPORT attempts to show how the eccentric position of the heart in the trunk is the cause for much of the observed difference between the vectorcardiograms registered by the different lead systems. Anatomically the heart lies to the left of, superior to, and anterior to the center of the trunk. For the experimental part of the investigation we have used newborn infants because their hearts appear to have a marked degree of eccentricity¹ and because of our previous work with this age group.^{2,3,4} In this investigation, only the QRS phase has been considered because the ventricles are more eccentric than the atria; also, its graphic characteristics are more suitable for analysis than the other phases of the heart cycle.

In the development and application of the methods used for the analysis, we have assumed that the body is a volume conductor whose size is large compared to the size of the heart and whose tissues possess a uniform conductivity. We also assume that the electrical activity of the ventricles is condensed into the center of the ventricular mass. The latter point is the anatomic location of the center (or pivot) of the heart vector.

These assumptions represent very rough approximations. They are justified by the practicality of the results. A preliminary analysis such as this would be overcomplicated by an attempt to correct for all the complexities of the human body at once.

A comparison will be made of the two lead systems which are commonly used to record the vector loops, namely the cube system of Duchosal and Sulzer, and the tetrahedral system of Wilson and Johnston.^{5,6} In the cube system Lead A serves as the horizontal lead, Lead B as the sagittal, and Lead C as the vertical; in the tetrahedral system, Lead I is the horizontal lead, Lead V₈ the sagittal and Lead aV_F the vertical. The two systems in the ideal form are diagrammatically shown in Fig. 1.

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Abbreviations used are:

- V_0 : the true spatial vector as would be manifested by an ideal system.
 V_c : the true spatial vector as would be manifested by the cube system.
 V_t : the true spatial vector as would be manifested by the tetrahedral system.
 X_0 : the effective axis of the horizontal lead of an ideal system; equal to the anatomic axes of Leads I and A.
 X_c : the effective axis of Lead A, the horizontal lead of the cube system.
 X_t : the effective axis of Lead I, the horizontal lead of the tetrahedral system.
 Y_0 : the effective axis of the vertical lead of an ideal system; equal to the anatomic axes of Leads aV_F and C.
 Y_c : the effective axis of Lead C, the vertical lead of the cube system.
 Y_t : the effective axis of lead aV_F , the vertical lead of the tetrahedral system.
 Z_0 : the effective axis of the sagittal lead of an ideal system; equal to the anatomic axes of Leads V_s and B.
 Z_c : the effective axis of Lead B, the sagittal lead of the cube system.
 Z_t : the effective axis of Lead V_s , the sagittal lead of the tetrahedral system.

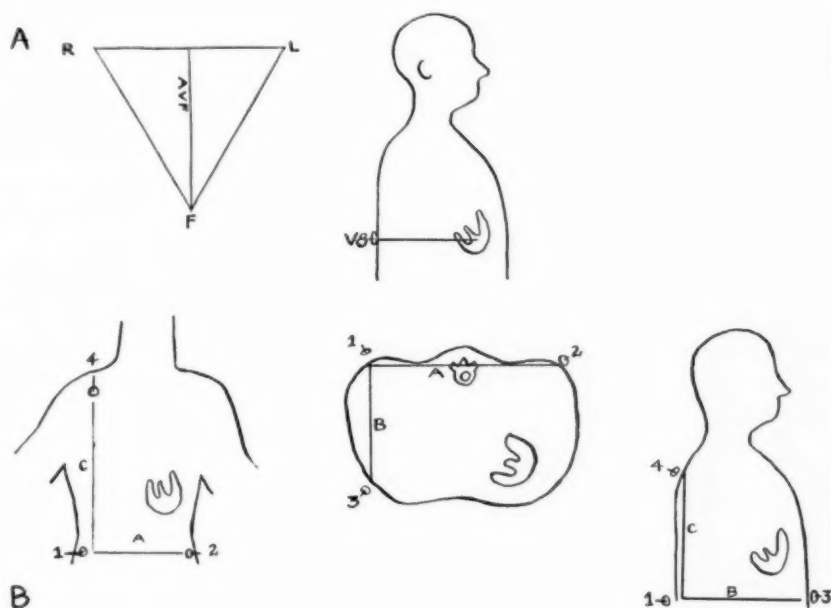


Fig. 1.—Diagram of the ideal state of the cube and tetrahedral lead systems.

A, Tetrahedral system. The equilateral Einthoven triangle with the heart in the center is the basis. Leads I and aV_F (or V_F) are the horizontal and vertical components. Lead V_s , the sagittal lead, is taken from the back, 3 cm. (in the adult) to the left of the spine and at the level of the seventh dorsal vertebral spine. It lies directly posterior to the ventricular mass.

B, Cube system. Electrodes numbers 1, 2, 3 are at the level of the second lumbar vertebra. Number 1 is in the right posterior axillary line, number 2 in the left posterior axillary line, number 3 in the right anterior axillary line; number 4 lies directly above number 1 in the suprascapular region so that the estimated site of the heart is equidistant from number 1 and number 4. Lead A equals 2 minus 1; it is the horizontal lead. Lead B equals 3 minus 1; it is the sagittal lead. Lead C equals 1 minus 4; it is the vertical lead. A positive deflection in each of these leads indicates that the heart vector has a component which points to the left, anteriorly, and down, respectively. Note that the leads are poled similar to the tetrahedral system, except that V_s is poled opposite to Lead B. A positive deflection in V_s indicates a posteriorly directed vector. Therefore the reciprocal of V_s is the homologue of Lead B.

The leads are so poled that an upright deflection in Leads I and A means that the heart vector points to the left; in Leads aV_F and C, it points inferiorly; in Lead V₈, it points posteriorly; and in Lead B, it points anteriorly.

The heart vector will be projected on the designated axis of a lead by dropping perpendiculars to the axis from the ends of the vector. The resulting projected image is responsible for the deflection registered by that lead.^{7, 8, 16}

For any given lead we shall distinguish between its anatomic axis and its electrically effective axis.

The anatomic axis of a lead is a line drawn from one component electrode to the other. For a bipolar lead it is a line from one electrode to the other. For a unipolar lead it is a line from the exploring electrode to the center of the vector. The latter point is theoretically at zero potential throughout the heart cycle.

If the electrodes of a bipolar lead are equidistant from the center of the vector (Fig. 2,A), then one may correlate perfectly the image projected on the anatomic axis with the recorded deflection in that lead. In such a case, the anatomic axis coincides with the effective axis.

If, however, the center of the vector is closer to one of the two electrodes of a bipolar lead, then the projection of the vector onto the anatomic axis does not correlate perfectly with the recorded deflection. In this case the anatomic axis cannot serve as the electrically effective one (Fig. 2,B).

A correlation between the projected image of an eccentric vector with the recorded deflection is still possible, provided one projects the vector on what may be called the effective axis of the lead. The effective axis of a lead may be defined as the line on which orthogonal projection of a vector agrees with the recorded deflection.

The effective axis of a lead can be found by means of a simple maneuver when eccentricity is the determining factor. One tilts the anatomic axis so that the nearer electrode moves to a more remote position and the remote electrode to a nearer position (Fig. 2,C). In other words, the geometric representation reverses the anatomic status in regard to eccentricity. This tilted line serves as the axis of the lead for purposes of projection. The amount of tilt will not concern us here; only its general direction in relation to the anatomic axis will be involved.

The mathematical formulation of this maneuver is:

$$\tan \theta = \frac{Y(r_1^3 - r_2^3)}{X_1 r_2^3 + X_2 r_1^3}$$

This is equivalent to Selvini and associates' formula and construction.¹³ (See Fig. 2,D for an explanation of the symbols.)

Because this formula does not take into account the limited size of the volume conductor and the uneven conductivity of the tissues it cannot be used in a quantitative fashion. It serves only to express the trend.

The effective axis of a unipolar lead is a line drawn through the exploring electrode and the anatomic site of the Central Terminal. In the ideal

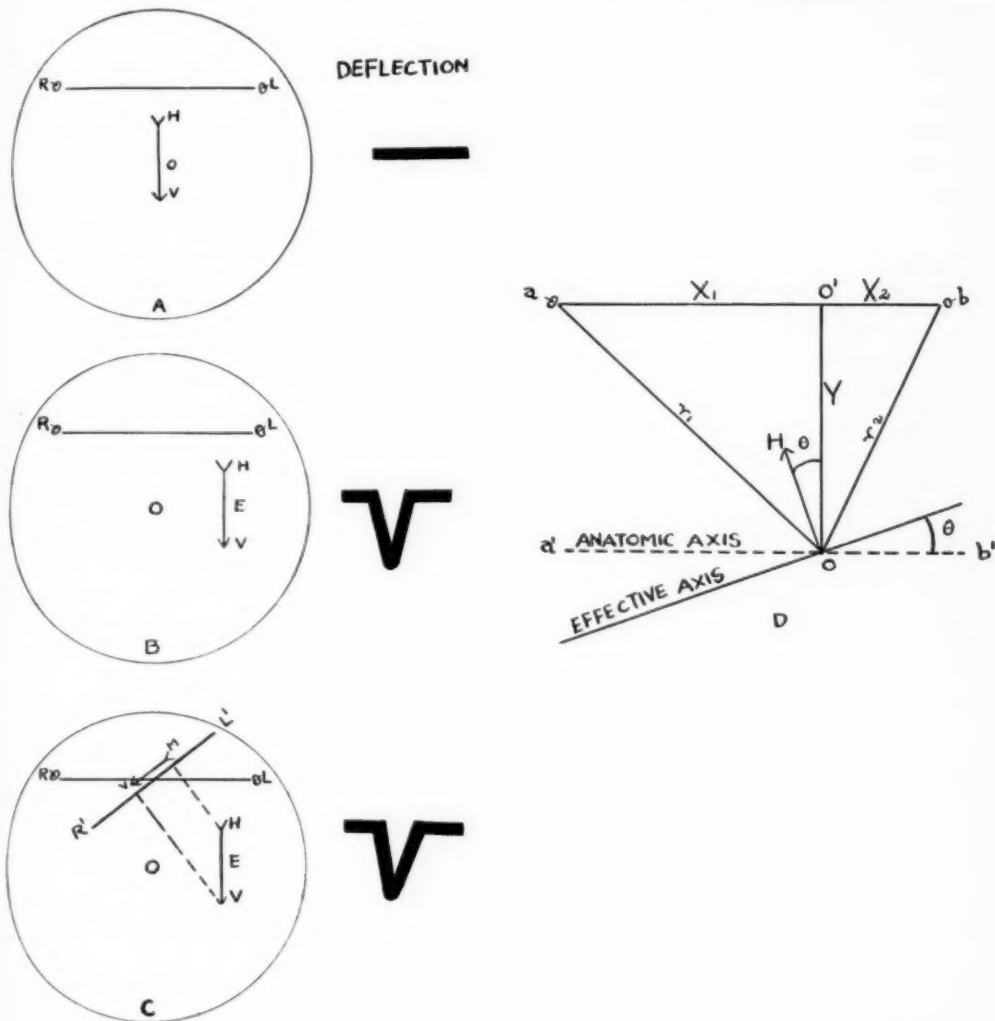


Fig. 2.—Anatomic versus effective axis of a lead. The circles represent a large volume conductor. The arrows are heart vectors which are truly perpendicular. The lead is one whose anatomic axis is truly horizontal, such as Lead I; *R* and *L* are the right and left arm electrodes. *O* is the center of the body.

A. Ideal case. The vector (*HOV*) centered in O is equidistant from *R* and *L*. The projection of *HOV* on *RL* is equal to a point. The registered deflection is zero and agrees with the projected image.

B. HEV, an eccentric heart vector, lies closer to *L* than *R*. Its projection on *RL* is also equal to a point. However the registered deflection is negative and does not agree with the projection on the anatomic axis.

C. The effective axis of Lead I is found by tilting RL so that L recedes from and R approaches HEV . The projection of HEV on $R'L'$ agrees with the registered deflection. $R'L'$ is the effective axis of Lead I.

D. Construction explaining the formula of the maneuver whereby the effective axis of a lead is determined by the eccentricity factor. The angle Theta measures the deviation of the effective from the anatomic axis. It is equal to the angle between a vector which is perpendicular to the anatomic axis and a vector which is perpendicular to the effective axis. This relationship permits the derivation of the following formula:

$$\tan \theta = \frac{Y(r_1^3 - r_2^3)}{X_1 r_2^3 + X_2 r_1^3}$$

HO is the positive one-half of the heart vector which is perpendicular to the effective axis.

ab is the anatomic axis; $a'b'$ is the anatomic axis transposed to the center of the system.

y is the perpendicular from O to the anatomic axis intersecting the latter at O' . x_1 and x_2 are the distances from the electrodes to O' .

r_1 and r_2 are the distances from the electrodes to O .

system the latter coincides with the centers of the heart and the body. This coincidence is not valid when the heart is eccentric. It has been adequately demonstrated^{1, 9, 16} that when the heart is closer to a given limb (in this case the left arm) the potential of the Central Terminal is dominated by the potentials of this limb. This implies that the Central Terminal is not at zero potential throughout the heart cycle. Rather, it varies with the potential of the proximal limb. The center of the vector and the center of the heart mass being at zero potential throughout the cycle would not be the site of the Central Terminal. The latter is located between the center of the heart mass and the proximal limb. In other words the anatomic site of the Central Terminal is always more eccentric than the heart. Therefore, the geometric site of the Central Terminal should lie between the left shoulder and the center of the myocardial mass of the ventricles. This point is joined with the exploring electrode to give the effective axis of the unipolar lead.

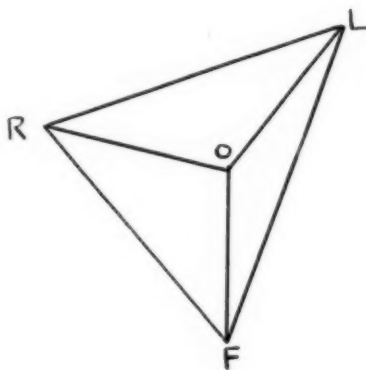


Fig. 3.—Burger Triangle applicable to the average adult. Note that the effective axis of Lead I, RL , is tilted counterclockwise from the true horizontal; the effective axis of V_F (and also aV_F) is tilted clockwise from the true vertical.

Only the direction of the lead axis will be discussed. The length of the axis is important for the correlation between the projected image of the vector and the magnitude of the recorded deflection. The length of the effective axis is directly proportional to the length of the anatomic axis and inversely proportional to the distance between the heart and the anatomic axis. This aspect of the problem will be neglected in this report.

Burger and van Milaan¹⁰ determined the effective axes of the limb leads experimentally on a model which simulated the human body. The direction and length of the lead axes were determined as functions of both eccentricity and conductivity of the different body tissues. The result is a triangle which is called the Burger triangle. Figure 3 shows the Burger triangle of the average adult. Wilson and associates confirmed this work experimentally; they elaborated and extended it theoretically.^{11, 12} Selvini and associates¹³ indicated the maneuver which permits the determination of the relative direction of the effective axis on the basis of the eccentricity factor.

We can now determine the relative direction of the effective axes of those leads which make up the cube and tetrahedral vectorcardiographic systems. Only the eccentricity factor will be used.

Eccentricity is such that the center of the heart and its vector lie to the left of, superior to, and anterior to, the center of the body.

The effect of this eccentricity on the axes of the different leads is shown in Fig. 4.

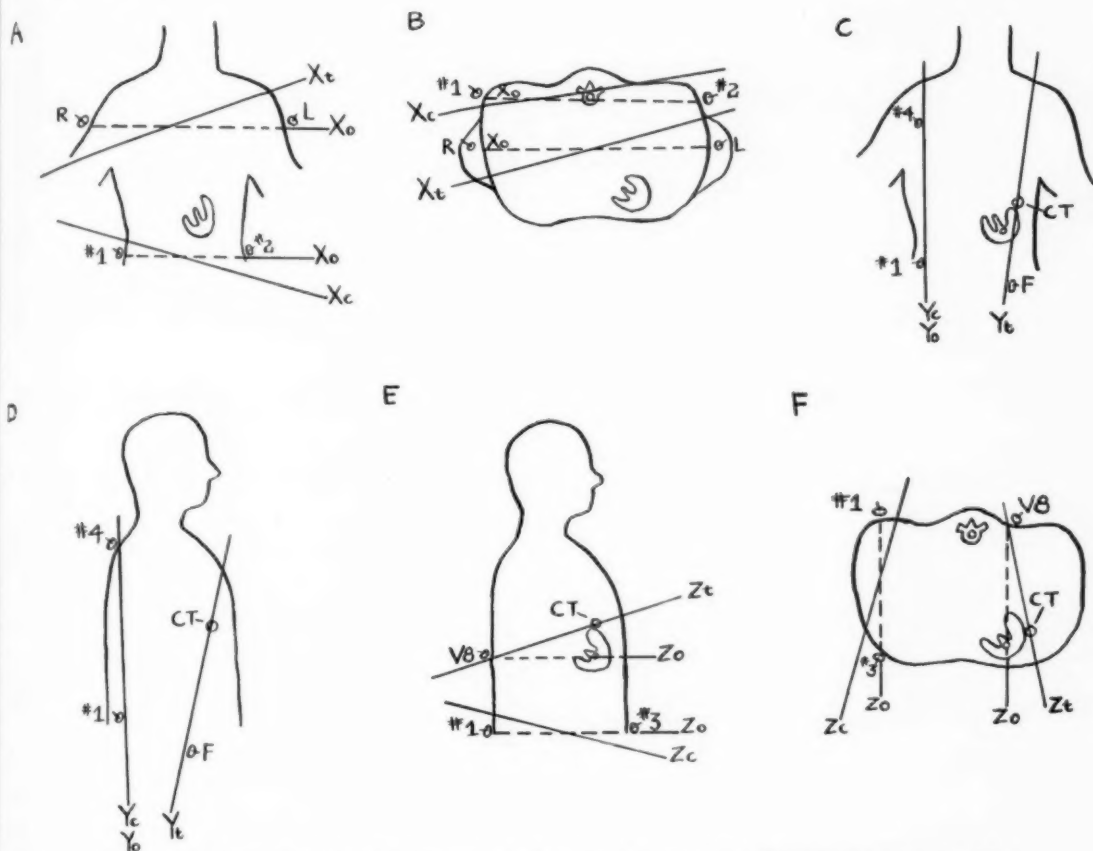


Fig. 4.—The direction of the effective axes as a function of eccentricity of the heart. The ventricles lie to the left of, anterior to, and superior to the center of the body. The central terminal, CT, in turn, lies to the left of, anterior to, and superior to the ventricles. The effective axes of the cube and tetrahedral systems are compared with each other and with the anatomic axes. The diagrams do not show the amount of deviation of the axes accurately. There is no reliable way for quantitating this, although it is our impression that Z_c and Z_t deviate from each other the most, and Y_c and Y_t the least. Electrodes are labelled as in Fig. 1; see text for other abbreviations.

A. The deviation of the horizontal axes within the frontal plane. Note the opposite tilt of X_t and X_c from X_o .

B. The deviation of the horizontal axes out of the frontal plane. Note that neither X_c nor X_t is a truly frontal lead.

C. The deviation of Y_t from Y_c and Y_o in the frontal plane. Since Y_c can be assumed to be parallel to Y_o , the latter is not shown in 4, C or 4, D. The direction of Y_t agrees with that of V_f in the Burger triangle.

D. The deviation of Y_t out of the frontal plane.

E. The deviation of Z_t and Z_c from Z_o . Z_t deviates because CT is even more eccentric than the heart itself.

F. The deviation of Z_t and Z_c out of the sagittal plane.

The proximity of the heart vector to the left electrode of Leads I and A causes the effective axes of these leads to be tilted from Xo in the manner indicated in Fig. 4, *A* and *B*. In the frontal aspect Xt and Xc are tilted from Xo in opposite ways; in the horizontal view they are tilted in the same direction so that the left ends of both axes lie more posteriorly.

The position of the Central Terminal to the left and anteriorly of the body's center causes Yt to be tilted so that its upper end lies to the left and anteriorly, as shown in Fig. 4, *C* and *D*. This agrees with the direction of the axis of V_F in the Burger triangle (Fig. 3).

Electrode number 4 is placed so that the heart is equidistant from it and number 1. Therefore, Yc may be considered to be ideal and parallel to Yo .

Zt has the tilt shown in Fig. 4, *E* and *F*, because the site of the Central Terminal is even more eccentric than the heart itself. The anterior terminus of Zt lies superiorly and to the left.

The proximity of the heart to the anterior electrode (number 3) of Lead B causes the axis Zc to be tilted in a manner opposite to that of Zt .

Note that the deviation of a given effective axis takes place in two planes. For instance Yt is so deviated that its lower end is displaced not only to the right but also posteriorly. The loops which are inscribed by these leads cannot be pure plane loops; that is, they are not the projection of the spatial loop on the designated plane. When the frontal loop is registered the record shows a loop which is partly frontal and partly sagittal. This applies to both systems.

These theoretical constructions can be verified and applied with the aid of two methods: the method of discrepant angles, and the method of deviating manifest vectors.

THE METHOD OF DISCREPANT ANGLES

The waves registered by two leads whose effective axes are parallel are identical as to polarity because the projections of a given vector on parallel lines are identical. The magnitude of the deflections may be unequal because they are a function not only of the size of the projected image but also of the length of the effective axis of the lead.¹⁰⁻¹²

If two leads have parallel anatomic axes then they are expected to register identically contoured complexes. For example, Leads I and A have horizontal anatomical axes, and for the most part they do record similar complexes. Certain differences have, however, been noted.¹ They can be explained only if the effective axes of these leads are determined. Then a construction as in Fig. 5 shows that those vectors lying in the acute angle formed by the perpendiculars to the two effective axes will inscribe discrepant deflections. All other vectors will register with equally poled deflections in the two leads. Fig. 6 shows the diagrams useful for the application of the method.

THE METHOD OF DEVIATING MANIFEST VECTORS

In vectorcardiography the leads are connected to the x and y plates of a cathode ray oscilloscope. The plates control the electronic beam and its light

spot on the screen. The spot represents the tip of the recorded vector. If the leads which are connected to the x and y plates are ideal in regard to direction and length, the spot's position will accurately indicate the tip of the vector. If the component leads are not ideal, the light spot will indicate a vector which does not coincide with the true one.

The construction in Fig. 7 indicates the manner in which the manifest vector will deviate from the true vector as a function of the deviation of the effective axis from the ideal or anatomic axis. The following relationships are to be noted:

1. The manifest vector deviates from the true vector in a direction opposite to the deviation of the effective axis of a lead from its anatomic (or ideal) axis.
2. Those vectors lying in the sector perpendicular to the anatomic (ideal) and effective axes suffer the greatest deviation.
3. Those vectors which bisect the acute angles made by the effective and anatomic (ideal) axes are not deviated at all.

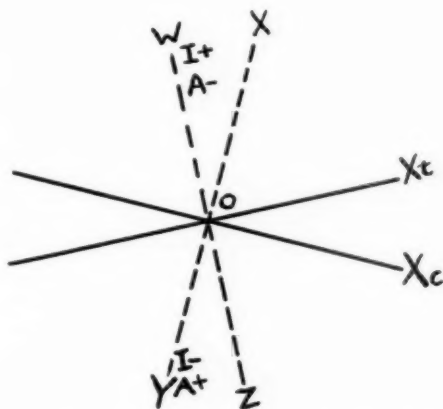


Fig. 5.—Angles of Discrepancy. X_t and X_c are the effective axes of Leads I and A. wz and xy are the respective perpendiculars to these axes. Both axes are transposed to the center of the body O for ease of construction. All vectors lying in the angle wox will project positively on Lead I and negatively on Lead A. All vectors lying in angle yoZ will project just the reverse. All other vectors will give the same type of deflection in both leads.

The mathematical formulation of the construction is:

$$\tan \alpha' = \frac{\tan \alpha_0}{\cos \beta + \sin \beta \tan \alpha_0}$$

α_0 = Angle made by true vector with ideal axis.

α' = Angle made by manifest vector with ideal axis.

β = Angle made by effective axis with ideal axis. (See also Fig. 7,C).

Figure 7 compares one nonideal lead with an ideal one. Since we do not have an ideal lead to serve as an experimental standard, we are forced to compare one nonideal lead with another nonideal lead. Accordingly, the construction in Fig. 7 must be modified as in Fig. 8. In Figure 8,A and 8,B each of the

X leads is compared with the ideal X axis. Also shown are the deviations of the manifest vector from V_0 . X_t deviates from X_0 counterclockwise; therefore V_t deviates from V_0 clockwise. X_c deviates from X_0 clockwise; therefore V_c deviates from V_0 counterclockwise. By combining Figs. 8,A and 8,B and by cancelling out X_0 and V_0 we obtain Fig. 8,C where X_t and X_c are compared and related to the relative direction of V_t and V_c . X_t deviates from X_c counter-

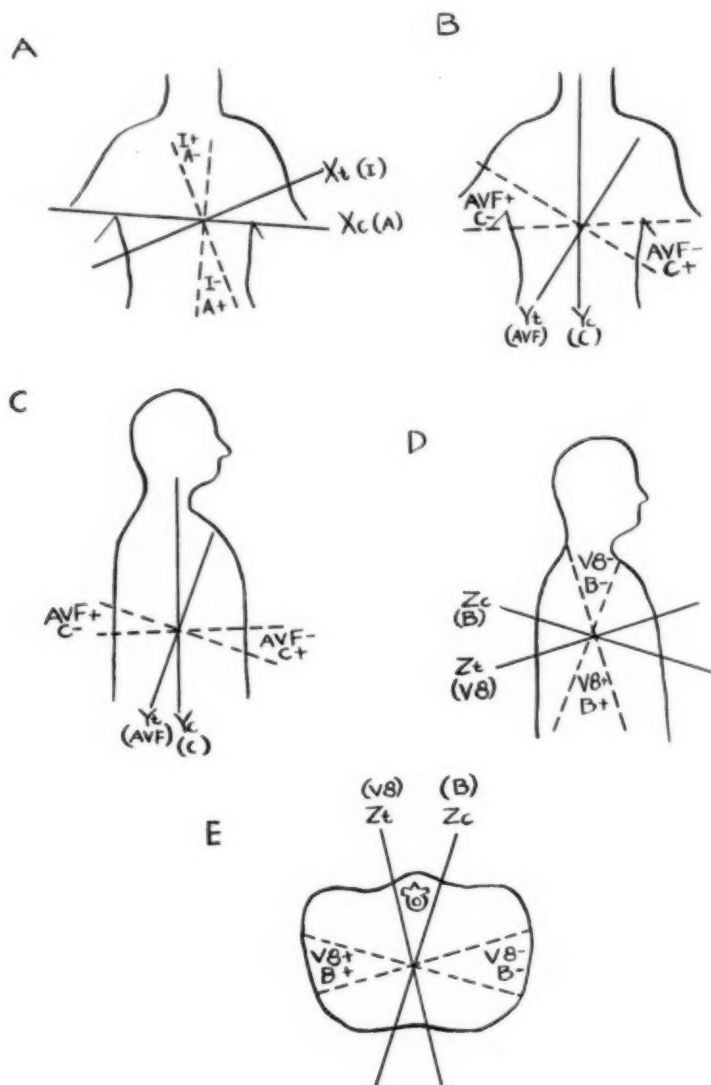


Fig. 6.—Application of the method of discrepant angles. If a segment of a vector loop can be identified with a particular electrocardiographic deflection and if the vector segment lies in the indicated angles of discrepancy then the corresponding leads should show discrepant deflections. Note that in Leads V_8 and B, waves of like polarity indicate discrepancy because the polarity of the circuit of V_8 is opposite to that of B.

clockwise; therefore V_t deviates from V_c clockwise. The general rule, applicable to the Y and Z axes also, states that the deviation of the manifest vectors will be in an opposite sense to the deviation of the effective axes of the leads.

The practical application of the above rule depends on the fact that the deviating lead axes exert their maximum effect on those vectors which lie in the sector perpendicular to these same lead axes. In the vectorcardiogram these vectors are represented by the segments of the loops which lie in this sector.

Figure 4 shows the relative directions of the effective axes of the leads of the cube and tetrahedral systems. Figure 9 shows the relative positions of the manifest vectors when V_o lies in the sector perpendicular to a given pair of lead axes.

Fig. 7

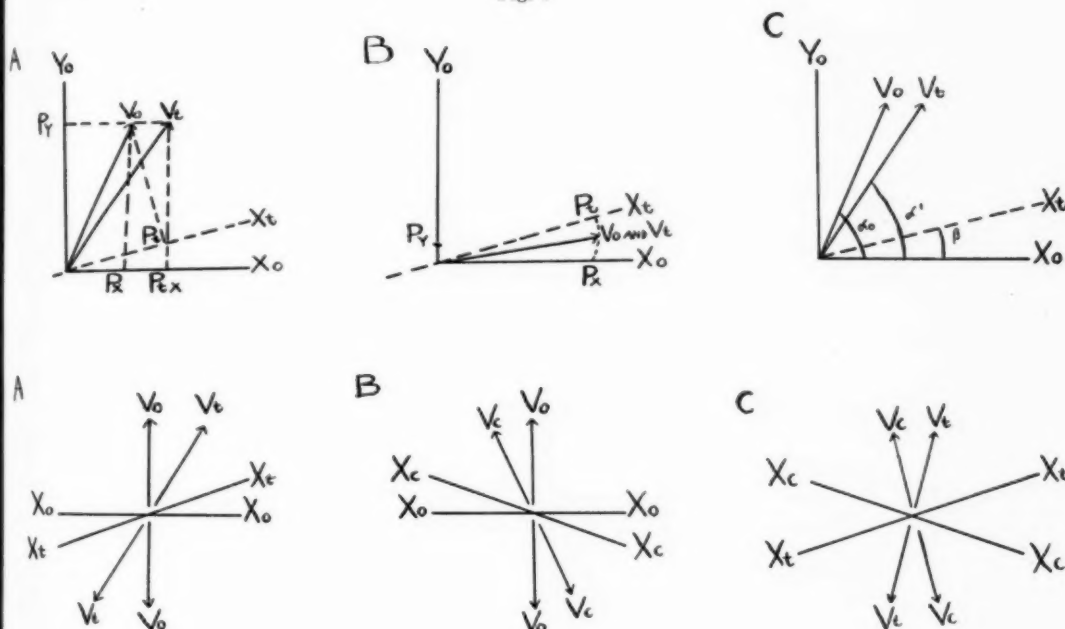


Fig. 8

Fig. 7.—The deviation of the manifest from the true vector as a function of the deviation of the effective from the anatomic lead axis.

A, Construction shows how the manifest vector deviates from the true in a sense opposite to the deviation of the effective lead axis from the anatomic. X_t deviates from X_o counterclockwise; this makes V_t deviate from V_o clockwise. X_o and Y_o are the axes of the ideal horizontal and vertical leads which are connected to the x and y plates of the cathode ray oscilloscope. V_o is the heart vector. The light spot on the screen representing the tip of V_o will have the coordinates P_x and P_y in accordance with the projection of V_o on X_o and Y_o . The manifest vector in this case is identical with the true one.

If Lead I is used as the horizontal lead then X_o must be replaced by X_t . We shall assume that Y_o remains as the vertical lead. From the construction it is seen that V_o projects on X_t with the length of P_t . Since this amount of potential is transferred to the x plates (represented by P_t which is equal in length to P_x) the light spot will have the new coordinates of P_y and P_t . The vector manifested is now V_t .

B, The effect of the lead axis deviation is minimized for those vectors which lie in the sector formed by the axes. In this case V_o bisects the angle which X_t makes with X_o . It projects with equal lengths on both; the x coordinate in the scope remains the same.

C, Angles used in the formula.

Fig. 8.—Construction showing how the cube and tetrahedral systems may be compared with each other with respect to the deviation of the manifest vectors as a function of the deviation of the effective axes.

A, The tetrahedral system compared with the ideal.

B, The cube system compared with the ideal.

C, The tetrahedral system compared directly with the cube by combining A and B and cancelling out the ideal system.

Each of the effective axes deviates from the ideal in two planes. This complication must be taken into consideration. For example, Fig. 9,E indicates that when V_0 points down, then V_t lies posteriorly to V_c ; Fig. 9,F indicates that when V_0 points to the right then V_t also points posteriorly to V_c . However, when V_0 points to the left then Fig. 9,F indicates that V_t will lie anteriorly to V_c . From this one can deduce that when V_0 points down and to the right, then V_t will be distinctly posterior to V_c ; but when V_0 points down and to the left, then it may not be possible to predict the relative positions of V_t and V_c .

The following Table I summarizes the expected correlations as derived from Figs. 6 and 9.

TABLE I. EXPECTED DISCREPANCIES BETWEEN THE CUBE AND TETRAHEDRAL SYSTEMS DUE TO ECCENTRICITY; BASED ON FIGS. 6 AND 9.

DIRECTION OF V_0	LOCATION OF V_t RELATIVE TO V_c	PARALLEL LEAD DISCREPANCY
Superior	Left	I positive A negative
Inferior	Right	I negative A positive
Right, posterior	Inferior	aV_F positive C negative
Left, anterior	Superior	aV_F negative C positive
Superior, left	Anterior	V_s negative B negative
Inferior, right	Posterior	V_s positive B positive

EXPERIMENTAL TECHNIQUE AND RESULTS

Twelve newborn infants were examined with both the cube and tetrahedral lead systems. All were normal in every respect except Cases 4, 11, and 12. Cases 4 and 11 showed the pattern of left ventricular preponderance with both lead systems;⁴ otherwise their physical status was normal and a follow-up examination one month later also showed normal findings. Case 12 was a newborn infant with cyanotic congenital heart disease.

In Cases 1 through 6 the following pairs of leads were recorded with a two-channel direct writing electrocardiograph (Twin-Viso Cardiette, Sanborn Company): I and aV_F , I and V_s , aV_F and V_s , A and C, A and B, and B and C. The tracings were made at a paper speed of 100 mm. per second. Coordinates for the construction of the planar loops were plotted every 0.005 second. In the plotting, the values of leads A and B were multiplied by 2 to correct at least partially for their low voltage which was due to the remoteness of their electrodes from the heart and the shortness of their lead axes. Other quantitative measurements were not made; they were not necessary because of the qualitative nature of the investigation.

In Cases 1 through 4 a simultaneous tracing of Leads I and A was taken. This was done by attaching the chest and left leg wires to the electrodes of Lead

A and the usual right and left arm wires to the electrodes of Lead I. In Cases 1 and 2, there was some difference in the appearance of the QRS complexes of Lead I when registered with Lead A and when registered with other leads such as V_8 and aV_F . The discrepancies were chiefly of a quantitative nature and involved the magnitudes of the deflections. They did not appreciably interfere with the present investigation. The characteristics of the electrocardiograph which are the cause of such artifacts are described by Lepeschkin.¹⁴

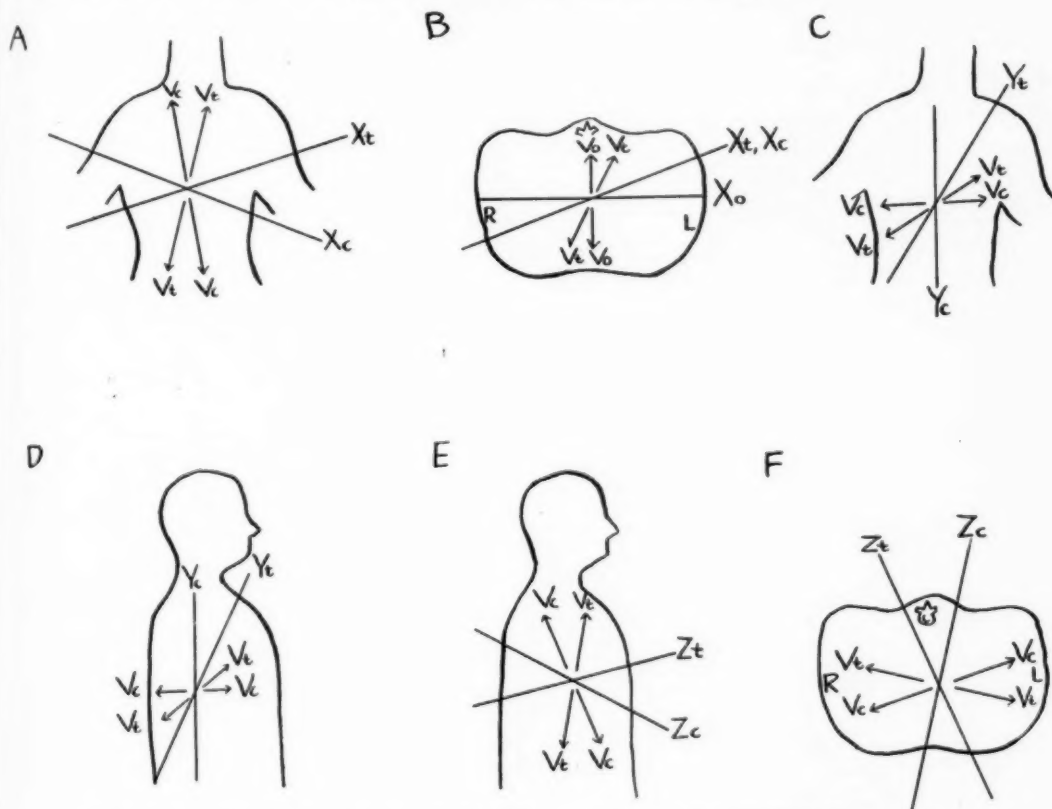


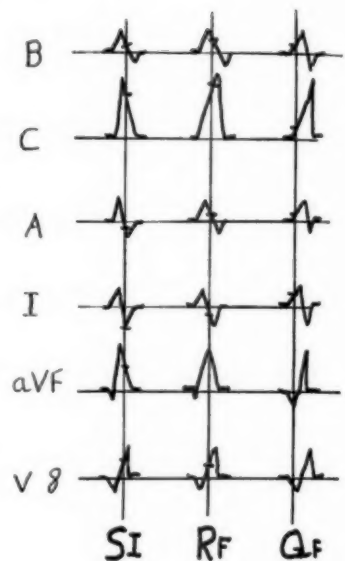
Fig. 9.—Shows the differences to be expected when a heart vector is registered by the two systems. Thus in A the prediction is made that when a vector is directed superiorly, V_c will lie to the right of V_t and when a vector is directed inferiorly then V_c will lie to the left of V_t .

The diagram in B differs from the others in that the deviation of both effective X axes in the horizontal plane is in the same direction with respect to X_o . Since we have no way for determining which is deviated more, X_t and X_c are shown to deviate equally from X_o . This construction indicates that neither lead system records a truly frontal planar loop. Both systems show a loop that is equal to the spatial loop viewed from the front and left.

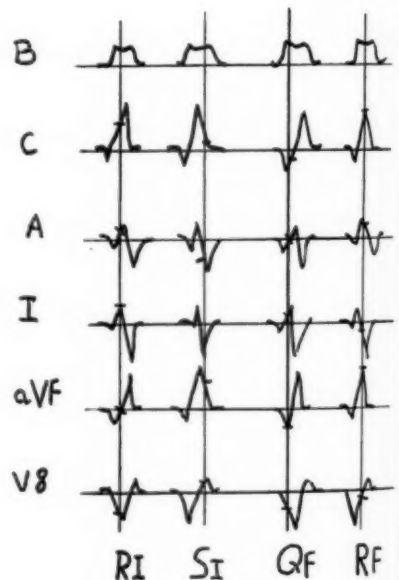
In Cases 1 through 4 the simultaneous record of Leads I and A permitted the determination of instantaneous vectors as manifested by both the cube and tetrahedral lead systems. Although the true vector (V_o) could not be ascertained, its manifestations V_t and V_c could. This was done by noting simultaneous points in Leads I and A; for example, a point in Lead A simultaneous with the peak of R in Lead I was determined. From the tracings of the other lead combinations it was possible to ascertain corresponding points in the com-

TABLE II.

CASE	DEFLECTION IN ELECTRO- CARDIOGRAM	POSITION OF Vt AND Vc	RELATION OF Vt to Vc	DISCREPANCY IN PARALLEL LEADS
1	Peak of S in Lead I	Vt—right, inferior, posterior Vc—right, inferior, anterior	Posterior	Vs positive B positive
	Peak of R in Lead aV _F	Vt—inferior, right, posterior Vc—inferior, left, anterior	Posterior and right	Vs positive B positive I negative A positive
	Peak of Q in Lead aV _F	Vt—left, anterior, superior Vc—left, anterior, inferior	Superior and left	aV _F negative C positive



2	Peak of R in Lead I	Vt—left, anterior Vc—left, anterior, inferior	Superior	aV _F isoelectric C positive
	Peak of S in Lead I	Vt—right, inferior, posterior Vc—right, inferior, anterior	Posterior and inferior	Vs positive B positive
	Peak of Q in Lead aV _F	Vt—superior, anterior, left Vc—superior, anterior	Left	I positive A isoelectric
	Peak of R in Lead aV _F	Vt—inferior, anterior, right Vc—inferior, anterior, left	Right	I negative A positive

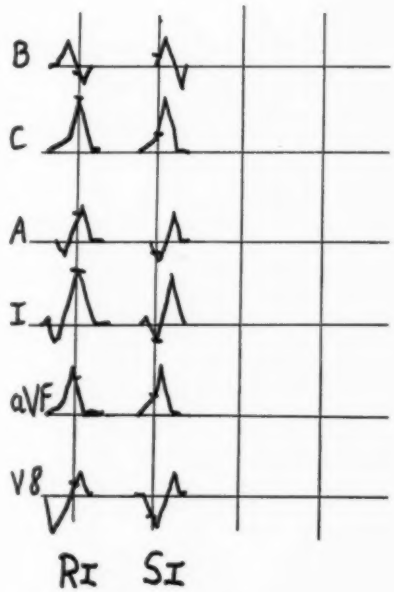
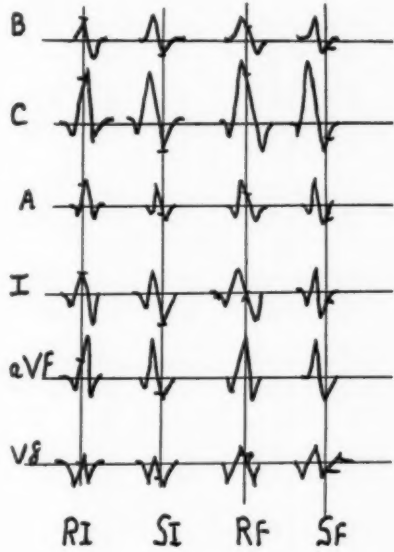


plexes of the other leads. These points in each lead, which may be accepted as being simultaneous with each other, could then be diagramed as in the last column of Table II. It was now a simple matter to describe the general characteristics of Vc and Vt. Their relative positions could be compared and the agreement with Table I determined.

The results are shown in Table II. Twelve pairs of discrepant instantaneous vectors could be accurately determined. The difference between Vc and Vt of each pair agreed with the principles summarized in Table I. Cases 1 and 4 are

TABLE II. (CONTINUED)

CASE	DEFLECTION IN ELECTRO- CARDIOGRAM	POSITION OF Vt AND Vc	RELATION OF Vt TO Vc	DISCREPANCY IN PARALLEL LEADS
3	Peak of R in Lead I	Vt—left, inferior Vc—left, inferior, anterior	Posterior and superior	Vs isoelectric B positive
	Peak of S in Lead I	Vt—right, superior, anterior Vc—right, superior, posterior	Anterior	Vs negative B negative
	Peak of R in Lead aVF	Vt—inferior, posterior Vc—inferior, left, anterior	Right and posterior	I isoelectric A positive Vs positive B positive
	Peak of S in Lead aVF	Vt—superior, right, anterior Vc—superior, right, posterior	Anterior	Vs negative B negative
4	Peak of R in Lead I	Vt—left, inferior, posterior Vc—left, inferior, posterior	Approximately equal	None
	Peak of S in Lead I	Vt—right, inferior, anterior Vc—right, inferior, anterior	Approximately equal	None



shown in Fig. 10. The dissimilarity between homologous loops is moderate in Case 1 and slight in Case 4. In other cases it was often much more marked. For Cases 7 through 12 the loops were drawn by hand on paper from their visualization on the screen of a vectorscope (Educational Cardioscope, Cambridge Instrument Co.). No corrections were made in the quantitative contributions of the component leads. Consequently the resulting cube loops were elongated vertically and compressed sagittally as compared to the loops constructed from the two-channel tracings. There was no opportunity in Cases 7 through 12 to register the component leads simultaneously on a two-channel apparatus.

Where a simultaneous tracing of Leads A and I was not available it was still possible to determine Vc and Vt, albeit in a crude way. An inspection of the planar loops often permitted an identification of segments as being synchronous in time. These segments could serve as Vc and Vt, and their relationships tested against the principles in Table I. Thus in Fig. 10, A the segments with like numbers are considered to be simultaneous and amenable to comparison. This method of analysis was used in cases 5 through 12. The results are not amenable to statistical detailing. In general they agreed very well with the Table I.

All twelve cases were analyzed by another method which was based on the same theoretical principles but with a different application. The method con-

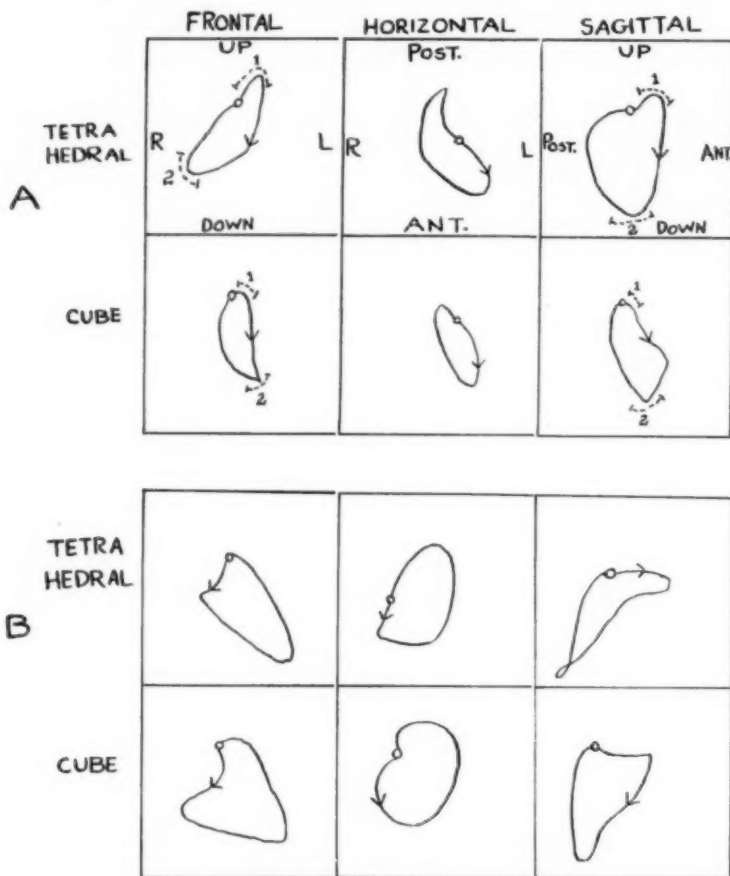


Fig. 10.—Vector loops of two newborn infants, registered by the tetrahedral and cube systems. Illustrates frequently found discrepancies between the two systems and the method for correlation.

A, CASE 1, a boy, 9 hours old. Loops show the usual type of right ventricular preponderance. Segment 1 is approximately simultaneous with the Q in aV_F, and segment 2 with the peak of R in aV_F. Segment 1 is located to the left and anteriorly. In accord with Table I the tetrahedral manifestation is superior to the cube and aV_F shows a Q while lead C shows an R deflection. Segment 2 lies inferiorly. Vt lies accordingly to the right and posteriorly of Vc.

B, CASE 4, a boy, 1 day old. The pattern is one of youthful left preponderance; infant was otherwise normal. The tetrahedral loops are located more posteriorly than the cube; otherwise there is little difference between the two systems. This can be ascribed to the fact that the loops lie in sectors which do not show marked differences when registered by both systems.

sists of the construction of a wire model of the spatial vector loops as registered by the cube system and then viewing the model as if the tetrahedral lead axes were the coordinates of the model.

First the spatial loop is constructed with wire from the frontal, horizontal, and sagittal loops which were inscribed by the cube system. One can reverse the process. To visualize the projection of the spatial loop on the frontal plane one views the model with one eye from the front and with the X and Y axes truly horizontal and vertical. To visualize the horizontal planar loop as inscribed by the cube leads one views the wire model from above with the X and Z axes truly horizontal and sagittal. Finally, to visualize the sagittal cube loop one views the model from the right with the Y and Z axes truly vertical and sagittal.

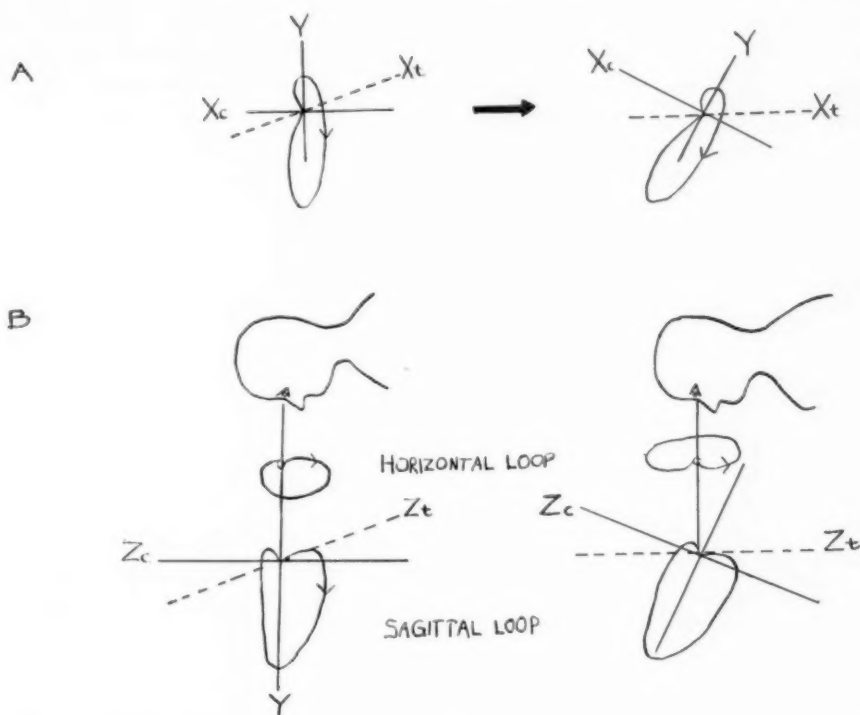


Fig. 11.—Diagrams of the maneuvers for visualizing the tetrahedral loops from the cube spatial loop. The cube loops were constructed by feeding the skew axes of the cube leads into the orthogonal axes of the recording apparatus. Therefore the orthogonal axes of the spatial cube loop are equivalent to the effective axes of the cube leads. This equating is necessary in order that the relative directions of the tetrahedral axes can be applied.

A. From Fig. 4 we know that X_t is deviated counterclockwise from X_c ; accordingly we can replace the X axis in the above diagrams with X_t . Now the entire loop is turned so that X_t becomes truly horizontal. The view from the front shows a loop with the characteristics of the tetrahedral frontal loop.

Note that the deviation of V_c from V_t is a function of the deviation of X_c from X_t ; note too the agreement with Table I and Fig. 9.

B. The same method applied to the Z leads. This graphically shows how the inferior segments of the loops are located more posteriorly in the tetrahedral system. It also indicates how the horizontal loops can appear so different yet be related. The observer views the spatial loop with one eye from above. He sees the horizontal planar loop. If the observer's line of vision is perpendicular to Z_c , he sees the cube horizontal loop. If it is perpendicular to Z_t , he sees the tetrahedral version of the horizontal loop

By a simple maneuver, it is also possible to obtain from the above cube spatial wire model a view of the planar loops as they are inscribed by the tetrahedral leads. First place on the origin of the loop an axis that has the direction of X_t . Then turn the entire loop so that X_t assumes a truly horizontal position. Viewing the loop with one eye from the front, one will see a planar loop as it would be inscribed by a horizontal lead with the axis of X_t , that is by Lead I. Since the tilt of the Y axis does not correspond to Y_t (it is in fact opposite to Y_t), the tetrahedral characteristics of the visualized loop are confined to the superior and inferior segments of the vector loop. Fig. 11 illustrates the maneuver. Note that this method is but another expression of the principles of Table I.

The method is especially useful for correlating the marked differences often found in the horizontal and sagittal loops of the two systems. This is done by placing Z_t on the origin of the loop and turning the entire wire model so that Z_t assumes a truly sagittal position. Then a view of the horizontal and sagittal planar loops will show the characteristics of the loops of the tetrahedral system (Fig. 11).

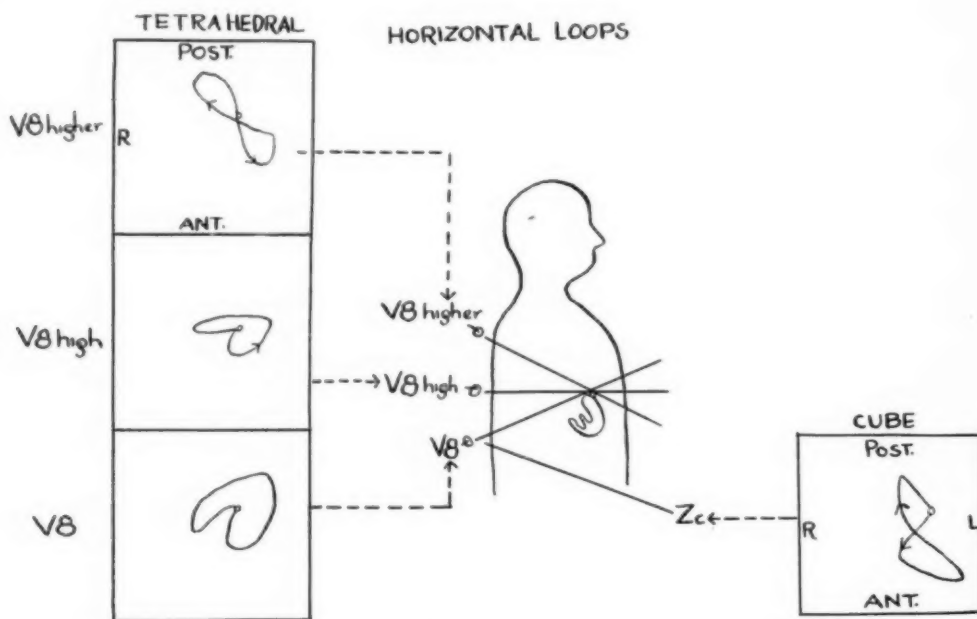


Fig. 12.—CASE 3, a girl, 8 days old. Horizontal loops. The tetrahedral horizontal loops were registered with three different sagittal Leads, V_8 , V_8 high, and V_8 higher, as shown in diagram. The exploring electrode for V_8 higher was on the upper one-half of the left scapula.

When the effective axes of the sagittal leads of the cube and tetrahedral systems are parallel, the horizontal loops are similar.

Wire models were made of the cube loops in all twelve cases. It was usually possible to obtain a convincing tetrahedral planar loop from each of them by using the effective axes of the tetrahedral system. This method was especially impressive when the tetrahedral horizontal and sagittal loops were seen as the model was turned to make Z_t truly sagittal.

If one could modify the tetrahedral system so that the effective axis of the sagittal lead paralleled that of Lead B, the resulting loops should resemble those of the cube. This was done by using a high V_8 . In all twelve cases as the exploring electrode ascended the left side of the back, the resulting horizontal and sagittal loops resembled more and more those of the cube system. The closest resemblance appeared usually when V_8 was taken from the upper part of the scapula. This affords additional evidence of the validity of the concept that the effective axis of Lead B is tilted with its dorsal end up. The results in Case 3 are illustrated in Fig. 12.

There is good evidence that the relative position of the lead axes of the two systems as described here for the newborn infant is valid also for the adult. In the book *Spatial Vectorcardiography* by Grishman and Scherlis²⁰ many of the illustrated cube loops are accompanied by the electrocardiographic records of the cube and tetrahedral leads. An examination revealed fifty-four instances where V_c and V_t could be identified and were discrepant; forty-nine showed agreement with Table I, five showed disagreement. There was also an illustration of a case of dextrocardia. In this case, the only discrepancy amenable to analysis indicated that the effective axes of Leads C and aV_F had a relationship opposite to that shown in Fig. 6.

DISCUSSION

Basic to this work is the negation of one of the main assumptions of both lead systems, namely, that the heart lies centric in the trunk. Also discarded was a modification of this assumption which stated that all electrodes more than 12 cm. distant from the heart were so remote that they could be considered as equidistant.

Recently two attempts have been made to justify this assumption of a centric heart.^{17,19} One group of investigators introduced a dipole into the retrocardiac esophagus,¹⁷ the other group into the right auricle. Both found good agreement between the actual and manifest direction of the vector. This is not unexpected inasmuch as the dipoles were in the midline and accordingly that much more centric than the ventricles which in this report are the source of the heart vector.

Burger and associates¹⁰ demonstrated experimentally the distortion of the record due to eccentricity and inhomogeneous conductivity. The results were confirmed by Wilson and associates;^{11,12} they also extended the theoretical aspects. Recently we showed how eccentricity interfered with the clinical application of Grant's method of vector analysis in the newborn infant;¹ also in the adult we showed how eccentricity was implicated in the discrepancies between so-called parallel leads.

Accordingly, the evidence appears adequate that eccentricity is a significant factor in the genesis of the electro- and vectorcardiogram. In this report, we have shown how eccentricity can be used to define the deviation of the effective axis and how the latter causes the manifest vector to deviate in an opposite direction. The subject has matured to the degree where its application is indicated not only in research but also in the clinic.

Since the factor of inhomogeneity of tissue conduction is less amenable to analysis, its consideration will be held in abeyance. Once it is evaluated, it can be readily translated into terms of eccentricity.

Our results indicate that eccentricity can account for many of the discrepancies between the loops of the two systems.

Research and clinical application of vectorcardiography will be seriously hampered unless a universal lead system is adopted soon.²³ The analysis of the different lead systems by the methods used here can be helpful in making a choice.

Neither the cube nor the tetrahedral systems can be considered as perfect or even near perfect. Furthermore one system cannot be said to be more accurate than another for there is no ideal reference system to serve as a measuring standard. Since it is impossible to evaluate the accuracy of a given system, the deciding factors are *practicality, reproducibility, and agreement with the electrocardiogram.*

The cube system has the disadvantage of employing leads and electrode placement that are not used in electrocardiography. They are inconvenient for both the patient and the technician. The reproducibility of the cube records is impaired by the unavoidable variation in the placement of each of the four electrodes in the same patient from one occasion to another. This was noticeable in the serial tracings of an infant with abnormal right preponderance due to congenital heart disease. This is a very important factor also in adult cardiography.

The unipolar chest leads appear to correlate much better with the cube loops than with the tetrahedral. This is used as evidence that the cube loops are more accurate.²⁰ To be sure, agreement between chest leads and loops is desirable. However, it is not necessarily evidence that the cube loops are more accurate. An examination of the relative directions of the effective axes of the unipolar chest leads is instructive.

The effective axis of a unipolar chest lead is a line drawn from the exploring electrode to the site of the Central Terminal, which has been shown above to lie to the left and superiorly of the center of the cardiac mass. Accordingly for the anterior precordial leads the effective axes will be tilted with their dorsal end up; this is parallel to Z_c , the effective axis of Lead B. On the other hand the posterior chest leads will have their effective axes tilted with the dorsal end down; this is parallel to the effective axis of V_8 . Consequently there will be better correlation between the anterior chest leads and the cube loops and between the posterior chest leads and the tetrahedral loops.

The correlation of the cube loops with the limb leads appears to be good but of course not as good as the tetrahedral loops whose components are the limb leads.

The tetrahedral system has the advantage of using the same electrodes and leads as in electrocardiography. The placement of the limb electrodes is convenient, fixed, and reproducible; however, the placement of V_8 is not fixed or reproducible. Furthermore the effective axis of V_8 appears to deviate from the true horizontal more than that of Lead B. Also disadvantageous is the poor correlation with the popular anterior precordial leads.

Can one modify the tetrahedral system so that its deficiencies are corrected and its advantages retained? This may be possible if a back lead could be found that has an effective axis more parallel to the anterior chest leads and whose electrode position could be more reproducible. It is logical to attempt to achieve this by using a unipolar back lead whose electrode is higher than that of V_4 . Although we have not carried out any systematic investigation as to its suitability it seems that a lead from the lower angle of the left scapula when the left arm lies adducted might be suitable.

It is logical to apply the eccentricity factor to the interpretation of the changes that arise from a change of position. It has been found repeatedly^{21,24} that the QRS axis shifts to the right in the left lateral position and to the left in the right lateral position as compared with the supine position. The effect of an increase or decrease of eccentricity on the effective axis of Lead I could easily account for such paradoxical findings. Pursuing the same line of reasoning it appears that the above behavior of the QRS axis should be seen only when the latter is pointing inferiorly. For vectors which point superiorly the deviation of the manifest axis should be the other way around. Furthermore, if Lead A (the horizontal lead of the cube) is used, the changes should be the reverse of those seen in the standard leads. We have obtained some confirmation of this in preliminary experiments.

In many cases of marked right ventricular preponderance the cube loop lies posteriorly.²⁰ This may be due to the fact that in these instances the loop is directed superiorly. An examination of Table I and Fig. 9 shows the tendency for superiorly directed vectors to be shifted posteriorly by the tilt of Lead B.

SUMMARY AND CONCLUSIONS

1. A distinction is made between the anatomic and effective axis of a lead. The anatomic axis of a lead is the line joining the anatomic sites of the component electrodes; for a unipolar lead the indifferent electrode is ideally located in the center of the heart. The effective axis is a line on which orthogonal projection of a heart vector agrees with the recorded deflection. There is a simple maneuver for determining the deviation of the effective from the anatomic axis as a function of eccentricity of the heart. One tilts the anatomic axis so that the nearer electrode moves to a more remote position and the remote electrode moves to a nearer position.

2. The deviations of the effective axes of the anatomically parallel leads of the cube and tetrahedral systems were determined. Homologous effective axes deviated usually in opposite directions from the anatomic ideal.

3. Such axis deviations cause differences in the manifestations of a given vector by the two systems. The deviation of the manifest vector was shown to be in an opposite direction to the deviation of the effective axes. Those vectors lying in the sector perpendicular to the effective axes were most strongly deviated; those lying in the sector formed by the effective axes were deviated the least.

4. Those vectors lying in the angle formed by the perpendiculars to the effective axes registered positively in one lead and negatively in the other. Ideally they should register with equal polarity in anatomically parallel leads.

5. A diagram and table were set up which correlated the deviations of the effective axes of homologous leads with the differences in the manifestations of the two systems.

6. A group of newborn infants were examined with both systems. The manifest vectors showed certain differences which agreed very well with the expected differences as set forth in the above mentioned diagram and table.

7. It was concluded that eccentricity is significant not only in the newborn infant but also in the adult. It accounted for much of the difference between the vector loops registered by both systems.

8. These methods for treating the eccentricity factor could be applied to the following problems:

(a) The choice of a lead system for vectorcardiography. It was shown that neither system could be considered more accurate than the other. On the basis of practicality, reproducibility and agreement with the electrocardiogram a modified tetrahedral system appears to be preferable to the cube.

(b) The interpretation of the shift of the manifest vector due to changes in the position of the body.

(c) The explanation for the posterior orientation of the cube loops in marked right ventricular preponderance.

We wish to express our gratitude to Mrs. Babette Newburger for the excellent executions of the illustrations. We also wish to thank Dr. David Scherf and Dr. James W. Benjamin for their helpful encouragement.

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Clinical Reports

COARCTATION OF THE AORTA IN THREE MEMBERS OF A FAMILY

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IN AUGUST 1945, Stein and Barber¹ reported observations concerning three members of one family with congenital heart disease. The mother had coarctation of the aorta and the son and daughter were thought to have a persistent patent ductus arteriosus. The present report deals with the re-evaluation of this family and shows that all three persons had coarctation of the aorta. No previous reports of three members of one family with coarctation of the aorta are noted in the literature.

CASE REPORTS

CASE 1.—A 41-year-old white woman, the mother of the patients in Cases 2 and 3, gave a history of a heart murmur having been found in childhood, which was considered to represent congenital heart disease; but no limitations were ever placed upon her physical activities. She had known her blood pressure to be elevated since she was about 18 years of age. She was conscious of pulsations at the angles of her shoulders when she would lean back heavily against a chair, being able to feel her body being pushed rhythmically forward. Palpitation was occasionally present but not disturbing. The patient was subject to headaches and the feeling of flushing and warmth about her face. She had had three full term pregnancies without complications.

This patient provided a family history from her correspondence with relatives which is pertinent, although not subject to our verification. She stated that her father died at age 78 of heart trouble with high blood pressure and that his youngest brother died at age of 30 of heart trouble. The patient's mother died at age 76 of coronary thrombosis. The patient's sister, age 60, is in good health; but of four children, one died at age 8 of congenital heart disease with a massive hemorrhage, and one has a heart murmur and high blood pressure. The patient's brother, age 58, was well but has a granddaughter, 11 or 12 years of age with "heart trouble" and a grandson with a heart murmur. A brother, age 26, has congenital heart disease with a lifelong murmur and has had a recent "heart attack." Another sister is well but has one granddaughter who is thought to have a patent ductus arteriosus. The husband, age 46, has a "heart block." His father died at age 75 years and his mother is living and well, but had one "blue baby" which died in nine days.

Physical examination of this patient revealed a well developed, mildly obese adult woman, 62½ inches in height and weighing 147 pounds. Blood pressure in the right arm was 190/100 mm. Hg and in the left arm 220/116 mm. Hg. Pulses could not be felt in the femoral, popliteal, posterior tibial, or dorsalis pedis arteries. Blood pressure could not be detected in the lower extremities. Faint pulsations could be felt in the abdominal aorta. Gross arterial pulsations could be felt in the intercostal spaces, about the angles of the scapulae, and in the subclavicular

¹ From the Cardiovascular Section, Letterman Army Hospital, San Francisco, Calif.
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and supraclavicular areas bilaterally. The heart was not enlarged, but a systolic murmur was heard with maximum intensity over the base of the heart. This murmur began some 0.04 to 0.08 second after the first heart sound; it could also be heard very distantly in the interscapular area. No thrill was present.

Roentgenograms of the chest revealed the cardiac shadow to be normal in size and configuration. The aortic knob was not visualized. Notching was present along the inferior border of the ribs posteriorly from the fourth to the tenth ribs on each side (Fig. 1). The electrocardiogram showed sinus tachycardia and a prolonged corrected Q-T interval of 0.45 second (Fig. 2).

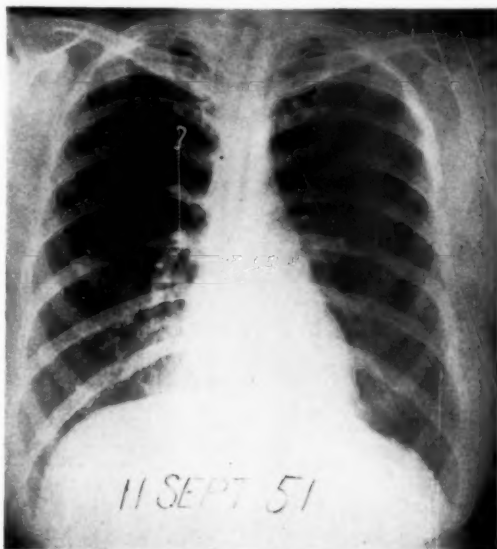


Fig. 1.—Roentgenogram of Case 1 showing notching along the inferior border of the ribs posteriorly from the fourth to the tenth ribs on each side. The aortic knob is not visualized. (Courtesy of Letterman Army Hospital Photographic Laboratory Neg. No. L-7131-2.)

CASE 2.—The 16-year-old daughter of the patient described in Case 1 was known to have had a systolic heart murmur since the age of one and one-half years. She had been considered to have a coarctation of the aorta since early life due to the presence of this defect in her mother and because of the poor arterial pulsations in her lower extremities. She had been restricted in her activities by medical advice but had not felt the need for physical restriction on the basis of symptoms. However, she was not active in sports and did not care to play with the vigor of other children of her own age.

Physical examination in January, 1951, revealed a well-developed, well-nourished young woman, 62 inches in height and weighing 116 pounds. Blood pressure in the left arm was 86/78 mm. Hg and in the right arm 100/74 mm. Hg. There was a very definite time lag in the pulse in the left arm as compared with the right. The femoral pulsations were weak. Pulses were not palpable in the popliteal and posterior tibial arteries, but there was a very faint pulsation of the dorsalis pedis artery bilaterally. Auscultatory blood pressure could not be obtained in the lower extremities, but by palpation pulsation in the right dorsalis pedis artery was felt up to 80 mm. Hg and on the left it could be felt up to 100 mm. Hg with maximum pulsation at 70 mm. Hg. The heart was moderately enlarged to percussion. Rhythm was regular. A systolic thrill was felt over the manubrium, and a systolic murmur with onset delayed about 0.06 to 0.08 second after the first heart sound was heard over the manubrium, to each side of the manubrium and over the neck vessels, particularly the left carotid artery where a thrill could be felt. This systolic murmur could also be traced along the paraspinal space from the level of the first through the eighth dorsal vertebrae.

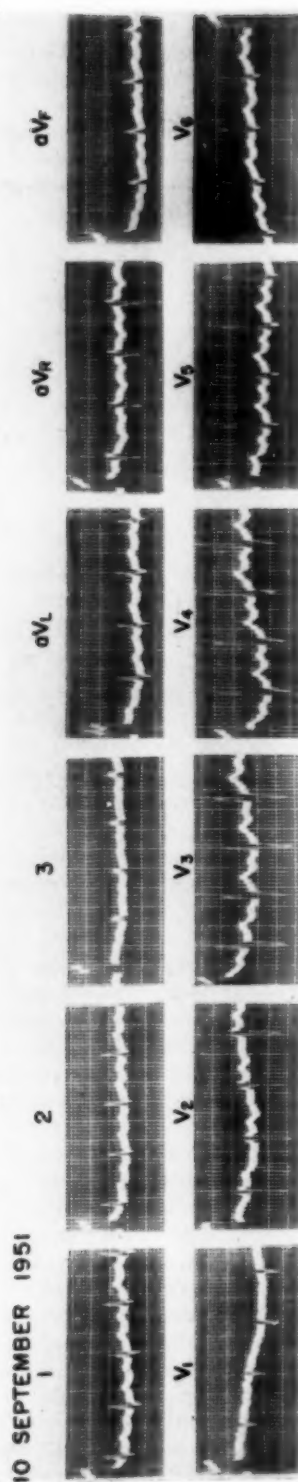


Fig. 2.—Electrocardiogram of Case 1 showing sinus tachycardia and a prolonged Q-T interval. (Courtesy of Letterman Army Hospital Photographic Laboratory. Neg. No. L-7131-1).

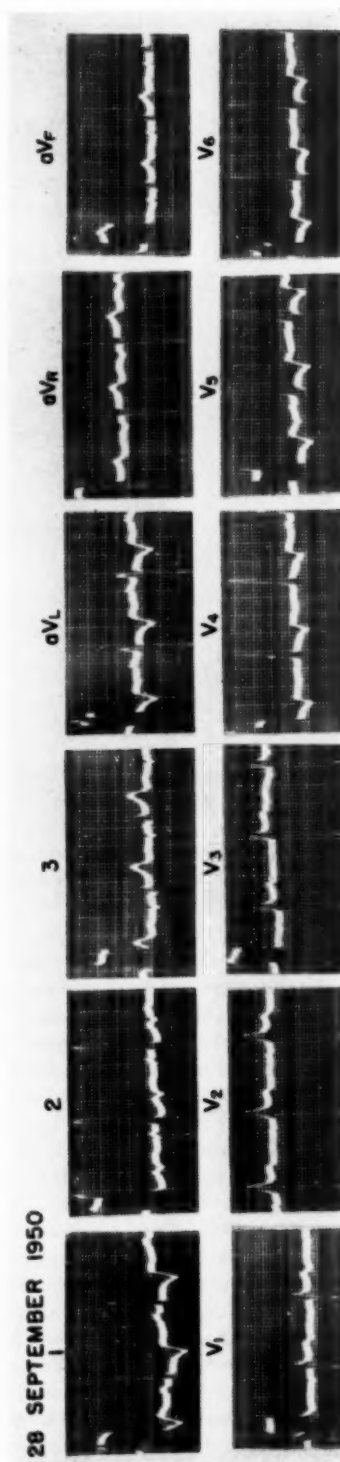


Fig. 3.—Electrocardiogram of Case 2 showing left ventricular strain. (Courtesy of Letterman Army Hospital Photographic Laboratory. Neg. No. L-7130-1).

Palpation at the angles of the scapulae revealed a faint pulsation and there were definite pulsations along the intercostal spaces from the third through the sixth intercostal spaces bilaterally. Pulsations were also noted in the supraclavicular area bilaterally and in the suprasternal notch.

The electrocardiogram was abnormal, showing depression of the S-T segment in standard Leads I and II and in Lead aV_L . Inversion of the T wave was present in standard Lead I and in Lead aV_L , and a diphasic T wave was noted in Lead II. The S-T segment was elevated in Leads III and aV_F . Precordial leads revealed depression of the S-T segment with inversion of the T wave in Leads V_4 , V_5 , and V_6 . This pattern was interpreted as "left ventricular strain" (Fig. 3).

Roentgenograms and fluoroscopic examination revealed moderate generalized enlargement of the heart due primarily to enlargement of the left ventricle. There was some increase in size of the hilar shadows bilaterally, but they did not show pulsatile expansion. The aorta appeared to be hypoplastic, and the aortic knob was not visualized. The ascending aorta was small, making the pulmonary conus appear prominent. The bony thorax appeared normal with no evidence of notching of the inferior borders of the ribs (Fig. 4).



Fig. 4

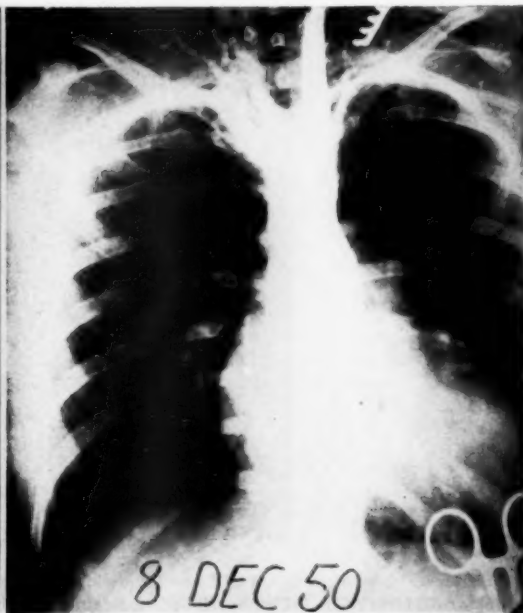


Fig. 5

Fig. 4.—Roentgenogram of Case 2 showing moderate generalized enlargement of the heart, due primarily to left ventricular enlargement. There is some increase in the size of the hilar shadows. The aortic knob is not visualized. There is no evidence of notching of the ribs. (Courtesy of Letterman Army Hospital Photographic Laboratory. Neg. No. L-7130-2).

Fig. 5.—Arteriogram of Case 2 showing a coarctation across the arch of the aorta affecting the origin of the innominate, the left carotid, and the left subclavian arteries. (Courtesy of Letterman Army Hospital Photographic Laboratory. Neg. No. L-7130-3).

An arteriogram made following the retrograde injection of iodopyracet into the left carotid artery showed coarctation across the arch of the aorta affecting the origin of the innominate, the left carotid, and the left subclavian arteries (Fig. 5).

CASE 3.—This patient was the son of the patient described above as Case 1. He was a 16-year-old high school student when seen in September, 1947, because of the family history of coarctation of the aorta. A systolic murmur was known to have been present from birth. The mother stated that she had never noticed him to be cyanotic. His mental and physical development were normal, and he was quite active in sports, including football and basketball, although he felt that he experienced more exertional dyspnea and fatigue than his teammates.

Physical examination at that time revealed a well-developed, well-nourished white man of adolescent age. Blood pressure in the left arm was 115/80 mm. Hg, in the right arm 138/85 mm. Hg, in the left leg 120/100 mm. Hg, and in the right leg 120/80 mm. Hg. The thorax was normally developed. Bounding pulsations and a definite systolic thrill were present along the carotid arteries. The heart was enlarged, with the apical impulse in the sixth intercostal space at the anterior axillary line. A systolic thrill was palpable over the manubrium and along its right border. In this area there was a loud rough systolic murmur which replaced the first heart sound, radiated over the entire precordium, and was transmitted to the neck vessels, down the course of the aorta and into the femoral arteries. The second aortic sound was virtually absent; the second pulmonic sound, however, was of normal amplitude. No unusual pulsations were felt along the course of the intercostal arteries. The femoral pulsations were very weak; the popliteal, posterior tibial, and the dorsalis pedis pulses were not palpable in either leg.

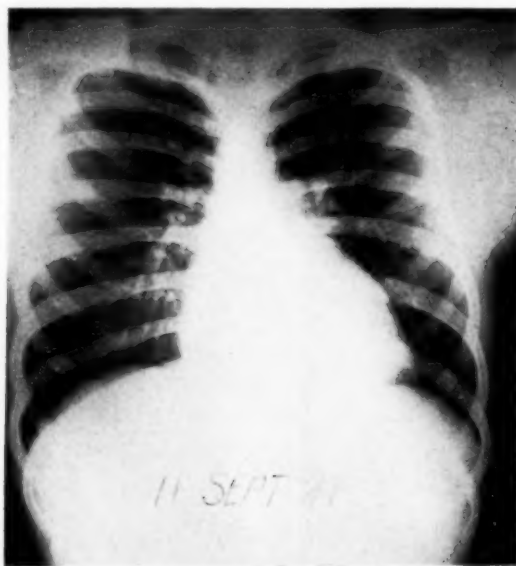


Fig. 6.—Roentgenogram of Case 3 showing enlargement of the heart, due primarily to left ventricular hypertrophy. The aortic knob is not visualized. (Courtesy of Letterman Army Hospital Photographic Laboratory. Neg. No. L-7129-1).

The roentgenogram of the chest and fluoroscopic studies revealed enlargement of the heart which involved predominantly the left ventricle. The aortic arch was not visualized (Fig. 6).

On May 12, 1948, while playing basketball in high school, this patient collapsed without warning and died. Autopsy* revealed a coarctation of the aorta with this vessel becoming abruptly stenotic immediately above the aortic cusps. Here the lumen was reduced to 3 to 4 mm. in diameter and the aortic circumference to about 3 centimeters. This stenotic lesion extended over the aortic arch past the origin of the left subclavian artery. More distally, the aorta appeared normal. The innominate and right common carotid arteries were enlarged and thick-walled; the left carotid artery appeared thick-walled but was rather small in caliber. The heart was tremendously enlarged, weighing an estimated 600 grams, primarily due to left ventricular hypertrophy. The left ventricular wall measured 2.4 cm. in thickness as compared to a right ventricular thickness of 0.6 centimeter.

*Appreciation is expressed to the Coroner, San Francisco, Calif., for the provision of the autopsy findings in Case 3.

DISCUSSION

Congenital heart defects occurring in several members of one family are not unusual. Eastman² states that if a malformation is present in one offspring there is a 20 per cent chance of some abnormality being present in subsequent offspring of the same mating and that there is a 2 per cent chance of those afflicted having the identical malformation. The presence of coarctation of the aorta, however, is unusual. The literature records only two such reports: Walker³ described a 48-year-old man and his 18-year-old son with the clinical findings of coarctation of the aorta, and Klemola⁴ wrote of two families in both of which two brothers had coarctation of the aorta as demonstrated by physical and roentgenologic findings.

Although the relationship of heredity to the familial occurrence of coarctation of the aorta must remain speculative, the three cases presented here provide support to the view that it may act as an etiological agent.

SUMMARY

Three cases of coarctation of the aorta occurring in one family and affecting the mother, daughter, and son are reported. This paper provides a follow-up on these cases, which were previously noted as examples of the familial occurrence of congenital heart disease.

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Book Review

VADEMECUM DER KLINISCHEN ELEKTROKARDIOGRAPHIE. By Schennetten, F.P.N. Leipzig, 1952, Georg Thieme. 119 pages, 64 figures.

This is the shortest primer of clinical electrocardiography yet published, the text (without illustrations) corresponding to approximately thirty pages of the size of this journal. The author states its primary purpose is "to give the practitioner, who receives the ECG interpretations from an electrocardiographer, some explanations about the most common terms and definitions (Begriffsbestimmungen) of electrocardiography." In his foreword, Brugsch goes farther and claims that this booklet incorporates all which is essential and might serve as a guide for electrocardiographic interpretation. Such extreme condensation would require very careful organization of the material and extensive use of tabular presentations. There are, indeed, several very good tables, summarizing the various abnormal patterns, but, as a whole, the organization of the material is very poor. Discussion of the fundamentals is limited to ten pages. Probably, the author feels that more would constitute theoretical ballast, unnecessary for the practitioner. Thus, the book consists essentially of a mere description of the most common abnormal patterns, without the guide of theory to explain their background.

The material is subdivided into the segments of the cycle (for instance, P wave, R wave, Q wave, S-T segment). This arrangement is inadequate for discussion of diagnostic electrocardiographic entities such as ventricular preponderance. Myocardial infarction is separately discussed under "R wave," "S-T segment," and "T wave." The inclusion of some abnormal T-wave patterns in the section "R-wave" adds further confusion. Bundle branch block is illustrated only by standard leads and discussed under "QRS complex" without reference to S-T and T changes. Chest leads and standard leads are treated separately. The best part of the book is the appendix about artefacts (19 pages). Only ten pages are devoted to all arrhythmias. Important examples have been omitted. There is, for instance, no illustration of ventricular tachycardia or fibrillation. It is unfortunate that most tracings of arrhythmias and bundle branch block do not have any time marks. In regard to terminology, the author differentiates Q, R, and S wave independent of the direction; he speaks of a positive Q or a negative R. He comments about the difficulty of differentiating a negative R wave from an S wave, but does not say how it can be done. He must be unaware of the fact that at opposite points of the body R and S wave are in phase. Adequate normal standards are missing. Within this small volume, the author has managed to incorporate a rather large number of erroneous or insufficiently substantiated statements, which cannot be discussed in detail. If used by a practitioner as a guide for interpretation, the book might do more harm than good, and Brugsch's recommendation in his foreword is somewhat surprising.

E. S.

Announcements

THE COOK COUNTY GRADUATE SCHOOL OF MEDICINE announces a two-week intensive course on "The Diagnosis and Treatment of Congenital and of Rheumatic Heart Disease in Infants and Children," presented by Benjamin M. Gasul, M.D., and Egbert H. Fell, M.D., and associates, from May 18 to May 30, 1953. For a circular giving full information, write to:

Registrar, Cook County Graduate School of Medicine, 707 South Wood Street, Chicago, Illinois.

THE AMERICAN COLLEGE OF CARDIOLOGY will hold its second annual convention at the Statler Hotel in Washington, D. C., June 7, 8, and 9, 1953. The topic will be Diagnosis of Cardiac Diseases. Any further information, pertaining to the program, may be obtained from the Secretary of the College, Dr. Philip Reichert, 480 Park Ave., New York 22, N. Y.